Dissertation on

"PREVALENCE OF HEPATOPULMONARY SYNDROME IN PATIENTS WITH CIRRHOSIS OF LIVER"

Submitted in partial fulfillment for the Degree of

M.D GENERAL MEDICINE

BRANCH – I

INSTITUTE OF INTERNAL MEDICINE

MADRAS MEDICAL COLLEGE

THE TAMIL NADU DR. MGR MEDICAL UNIVERSITY

CHENNAI – 600003

APRIL 2015

CERTIFICATE

This is to certify that the dissertation entitled "**PREVALENCE OF HEPATOPULMONARY SYNDROME IN PATIENTS WITH CIRRHOSIS OF LIVER"** is a bonafide original work done by **Dr. SYED ANSARI. J**, in partial fulfillment of the requirements for M.D. GENERAL MEDICINE BRANCH – I examination of the Tamilnadu Dr. M.G.R Medical University to be held in April 2015, under my guidance and supervision in 2014

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I hereby solemnly declare that the dissertation entitled "**PREVALENCE OF HEPATOPULMONARY SYNDROME IN PATIENTS WITH CIRRHOSIS OF LIVER"** is done by me at Institute of Internal Medicine, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai during 2014 under the guidance and supervision of **Prof. S.G. SIVACHIDAMBARAM M.D.,** This dissertation is submitted to The Tamilnadu Dr. M.G.R Medical University, Chennai towards the partial fulfillment of requirement for the award of M.D. Degree in General Medicine (Branch I)

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ACKNOWLEDGEMENT

I express my heartful gratitude to the Dean, **Prof. Dr. R. VIMALA M.D.**, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai-3 for permitting me to do this study.

I am deeply indebted to **Prof. Dr. S. TITO M.D**., Director i/c & Professor of Medicine, Institute of Internal Medicine, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai-3 for his support and guidance.

I am very grateful to **Prof. Dr. S.G.SIVACHIDAMBARAM M.D.,** Professor of Medicine, Institute of Internal Medicine, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai-3 who guided and trimmed my work throughout the period of my study.

I am very much thankful for the help rendered by my Assistant Professors **Dr. K. VIDHYA, M.D.,** and **Dr. J. JACINTH PREETHI M.D.,** for their constant help and encouragement.

I am very much thankful to **Prof. Dr. D. RANGANATHAN M.D.,** Head of the department, Department of Thoracic Medicine, Madras Medical College & RGGGH, Chennai for his support and guidance.

I am very much thankful to **Prof. Dr. RAVI M.D., D.M.,** Head of the department, Department of Cardiology, Madras Medical College & RGGGH, Chennai for his support and guidance.

I am extremely thankful to all the Members of the **INSTITUTIONAL ETHICAL COMMITTEE** for giving approval for my study.

I express my heartful gratitude to **Dr. M. SUDHA** and **Dr. P. KRISHNARAJAN** for their constant support and encouragement.

I also thank all the patients who were part of the study and my Professional colleagues for their support and criticisms

CONTENTS

ABBREVIATIONS

ABG	-	Arterial Blood Gas
ALT	-	Alanine aminotransferase
AST	-	Aspartate aminotransferase
AV	-	Arteriovenous
CPC	-	Child Turcotte Pugh classification
CT	-	Computed tomography
ET	-	Endothelin
eNOS	-	Endothelial nitric oxide synthase
FEV1	-	Forced Expiratory Volume in one second
FVC	-	Forced Vital Capacity
GGT	-	Gammaglutamyl transpeptidase
HE	-	Hepatic encephalopathy
HPS	-	Hepato Pulmonay Syndrome
HRS	-	Hepatorenal syndrome
L-NAME	-	N^G-nitro-L arginine methyl ester
LFT	-	Liver function test

MELD	-	Model for End stage Liver Disease
NO	-	Nitric oxide
OLT	-	Orthotopic liver transplantation
PaO_2	-	Partial pressure of oxygen
PAH	-	Pulmonary artery hypertension
PEFT	-	Peak expiratory flow rate
PFT	-	Pulmonary function test
PPH	-	Portopulmonary hypertension
RFT	-	Renal function test
SaO_2	-	Saturation of oxygen
SBP	-	Spontaneous bacterial peritonitis
TcMAA	-	Technetium 99m – labelled maroaggregated albumin
TIPS	-	Transjugular intrahepatic portosystemic shunt

“PREVALENCE OF HEPATOPULMONARY SYNDROME IN PATIENTS WITH CIRRHOSIS OF LIVER”

ABSTRACT:

INTRODUCTION:

Cirrhosis of liver is a very common disease which clinicians encounter both at primary and tertiary care. Development of pulmonary manifestations in cirrhosis has several clinical implications with regard to their management, since they carry a poor prognosis. These include pleural effusion, restrictive and obstructive lung disease, Hepatopulmonary syndrome and portopulmonary syndrome. Hepatopulmonary Syndrome (HPS) is a triad of liver disease, hypoxemia and intrapulmonary vascular dilatation. The reported prevalence of HPS in cirrhotic patients varies between 4% and 19%.

AIMS & OBJECTIVES:

- To study the pulmonary profile in patients with cirrhosis with reference to arterial hypoxemia.
- To detect the presence of hepatopulmonary syndrome among cirrhotic patients.

MATERIAL & METHODS:

Patients admitted in Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai with cirrhosis of liver, proven by clinical, sonographic and endoscopy evidence, fulfilling the inclusion and exclusion criteria were included in the study. Data was collected in a pretested proforma meeting the objectives of the study.

40 cases were selected on the basis of the simple random sampling technique. Emphasis was placed on the pulmonary complaints and its impact. Patients were investigated for Arterial blood gas analysis, Spirometry and Contrast Echocardiogram. Relevant Statistical methods were applied.

RESULTS:

In our study, Cirrhosis was common in young adults in the fourth decade with male to female ratio of 3:1. The most common respiratory system finding was right pleural effusion and it was the most common chest radiographic abnormality. Restriction was the most common abnormality in pulmonary function tests. Hypoxemia was present in 17.5% of cirrhotics, out of which 4 patients (10%) were found to have Hepatopulmonary Syndrome (HPS). Orthodeoxia was the characteristic feature of the patients who had HPS. All 4 patients with HPS presented

with cyanosis, orthodeoxia and spider naevi. Spider naevi could be a marker for the presence of intrapulmonary vascular dilatation.

CONCLUSION

The feature of our study was the detection of hypoxemia in patients with cirrhosis of liver. Degree of hypoxemia worsens with higher grade of varices. Severity of liver disease also worsens hypoxemia. Hepato pulmonary syndrome was seen in 10% of patients with cirrhosis. The prevalence of HPS is influenced by the severity of liver disease. The only proven treatment for HPS is liver transplantation. As prognosis of HPS is poor, screening for its presence in cirrhotic patients is very important.

KEYWORDS: Hepatopulmonary syndrome, Hypoxemia, Orthodeoxia, Contrast echocardiogram, arterial blood gas analysis.

INTRODUCTION

Cirrhosis of liver is a very common disease which clinicians encounter both at primary and tertiary care. Cirrhosis is associated with several complications and overall carries a poor prognosis. The management of cirrhosis includes early detection and treatment of various complications like hepatic encephalopathy, coagulopathy, ascites, hepatorenal syndrome etc. Recently there has been an increased interest in literature about pulmonary manifestations of cirrhosis of liver which are equally important and has been relegated to background both in Indian and western countries.

Development of pulmonary manifestations of cirrhosis has several clinical implications with regard to their management, since they carry a poor prognosis. Cirrhosis and portal hypertension are associated with pulmonary manifestations that affect the pleura, lung parenchyma, and pulmonary vasculature. Dyspnea and hypoxemia are the predominant presentations.

The pulmonary disease manifestations include pleural effusion, obstructive lung disease, restrictive lung disease, impairments of pulmonary gas exchange (Hepatopulmonary syndrome) etc.,[1]

Hepatopulmonary Syndrome (HPS) is a triad of

1) Hypoxemia
2) Pulmonary vascular dilatation
3) Liver disease

About 4% to 19% prevalence rate of HPS is observed in patients with cirrhosis.[2] Most cases have occurred in patients with cirrhosis & portal hypertension. The prognosis of HPS is poor in cirrhosis.

AIMS & OBJECTIVES

AIM & OBJECTIVES

- To study the pulmonary profile in patients with cirrhosis with reference to arterial hypoxemia.

- To detect the presence of hepatopulmonary syndrome among cirrhotic patients.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

In 1884 Fluckiger described the death of a middle aged woman with digital clubbing & cyanosis who died as a consequence of syphilitic liver disease, esophageal bleeding, and hepatic coma.[3] Postmortem examination showed abnormally dilated pulmonary vessels and thus led to the first description of a pulmonary manifestation of liver disease.

In 1959, Rydell & Hoffbauer provided the first clinical and postmortem documentation of what was to be later called hepatopulmonary syndrome by Knudsen and Kennedy in 1977.[4] The postmortem study showed both precapillary dilatation and direct AV communications following vascular injections with a solution of plastic vinyl acetate. In 1994, however, Krowka and Cortese consolidated the definition of HPS to be limited to an arterial oxygen tension of less than 70 mmHg.[1]

CIRRHOSIS OF LIVER:

Cirrhosis of liver is a histopathologically described condition. It presents with various clinical features & complications. Cirrhosis is usually irreversible. But when the underlying cause is removed, fibrosis can be

revered. This can be seen in chronic hepatitis C, hemochromatosis and alcohol liver disease.[5]

- In 1761, Gianbattista Morgagni, an anatomic pathologist, first identified the cirrhotic transformation of liver in his autopsy specimens.
- In 1826, Laennec coined the term "cirrhosis" - meaning orange color in Greek, due to the yellowish-tan color of the cirrhotic liver.[6]
- In 1930, Roessle described pathogenesis of cirrhosis → parenchymal degeneration, regeneration and scarring.

Cirrhosis is defined by three morphological characteristics in the liver[7]

1) Bridging fibrous septa
2) Parenchymal nodules
3) Architectural disruption of the liver

PATHOGENESIS OF CIRRHOSIS:

Pathogenic processes include

- Hepatocyte destruction,
- Extracellular collagen deposition
- Vascular reorganization

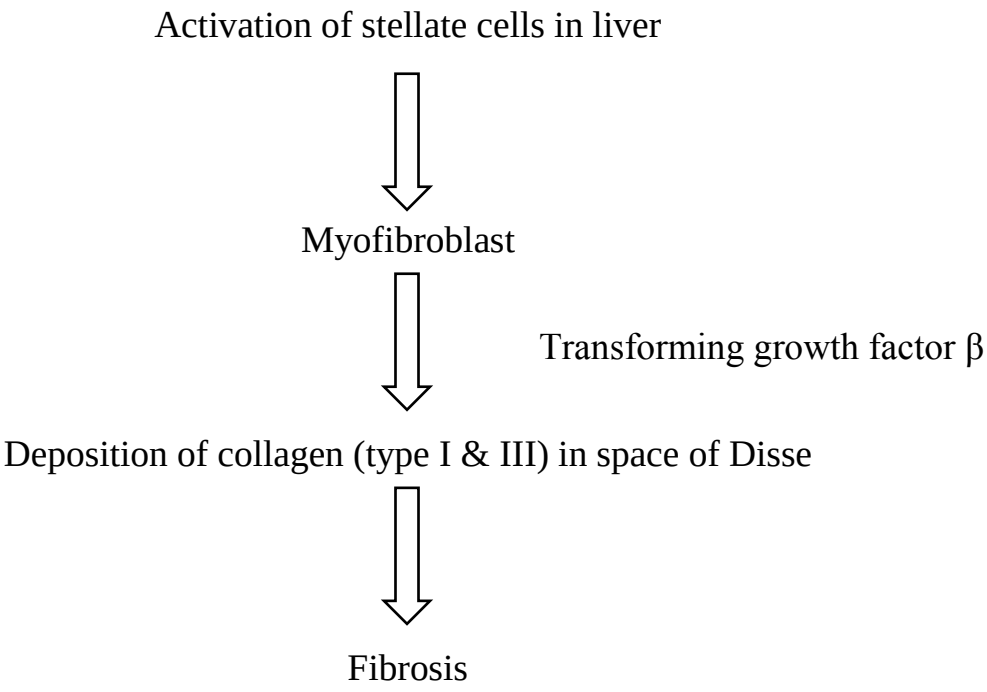
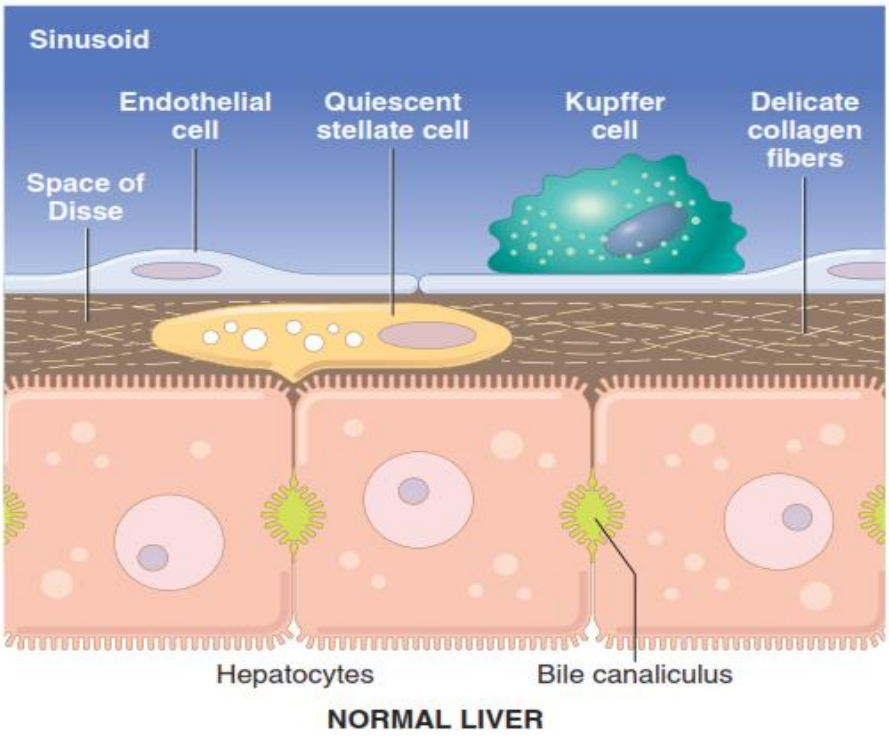


Figure1. Pathogenesis of cirrhosis



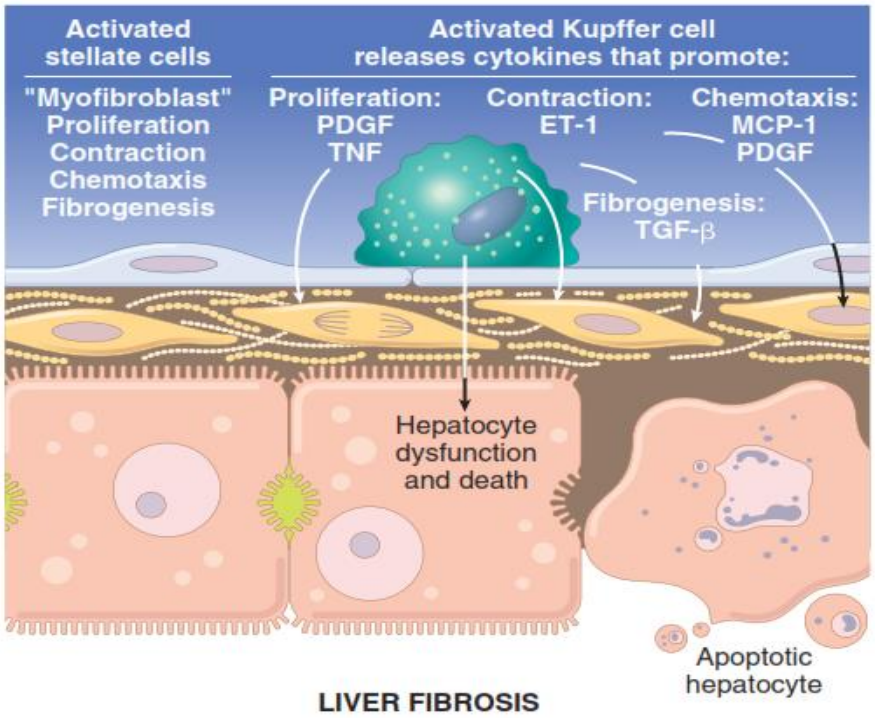


Figure 2: Cirrhosis of liver – gross pathology

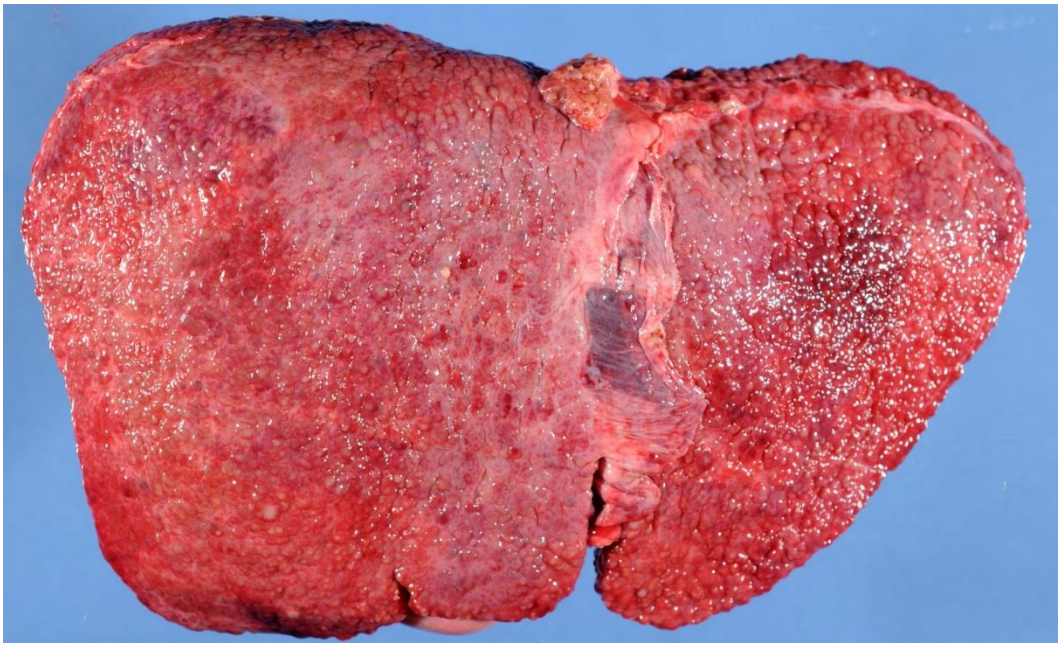
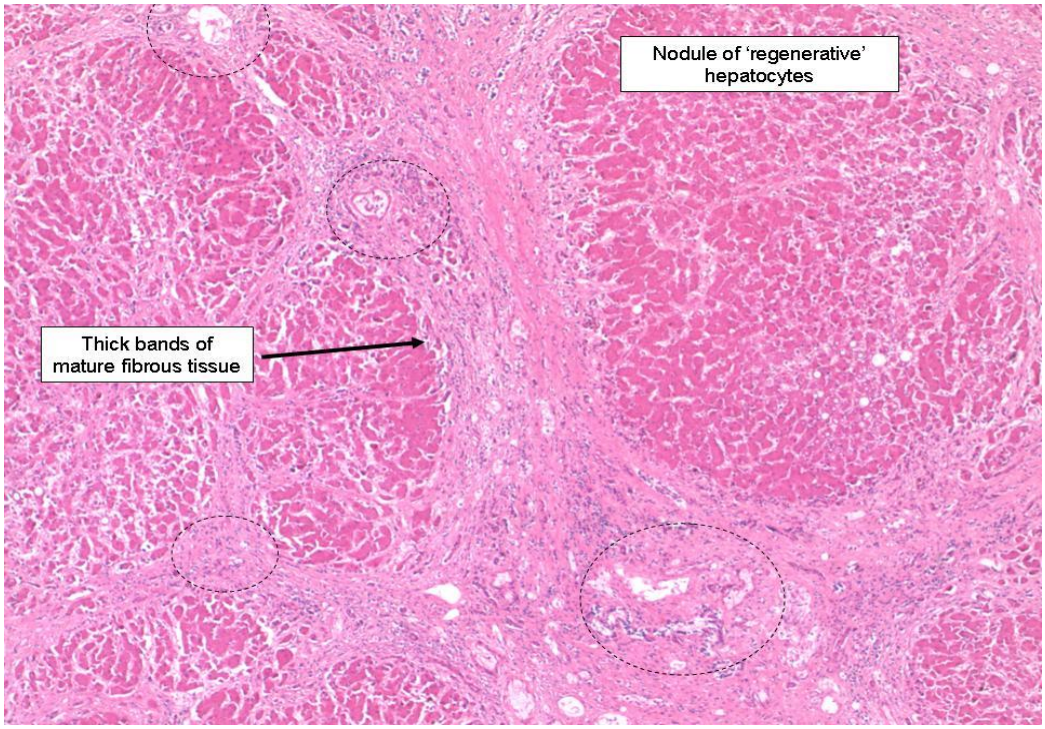
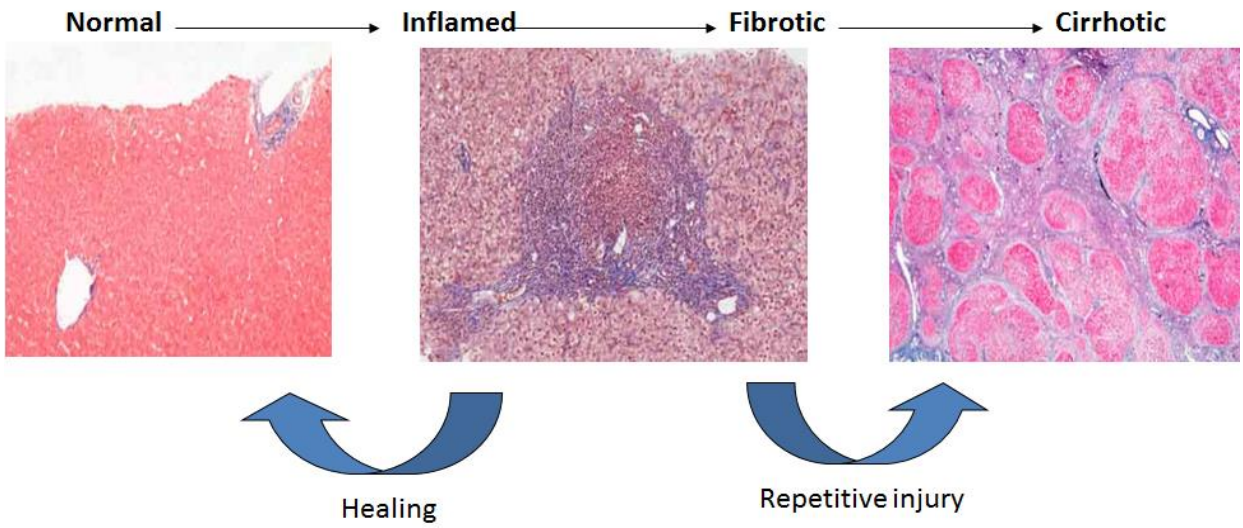


Figure 3: Cirrhosis of liver - Histology





CAUSES OF CIRRHOSIS:[5]

Alcoholism	Chronic viral hepatitis
Cardiac cirrhosis	Inherited metabolic liver disease
Hepatitis B	Hemochromatosis
Hepatitis C	Wilson's disease
Autoimmune hepatitis	α_1 Antitrypsin deficiency
Nonalcoholic steatohepatitis	Cystic fibrosis
Biliary cirrhosis	Cryptogenic cirrhosis
Primary biliary cirrhosis	
Primary sclerosing cholangitis	
Autoimmune cholangiopathy	

Prevalence of liver cirrhosis showed a marked geographic difference worldwide due to various etiology. Alcohol is the most common cause for liver cirrhosis.

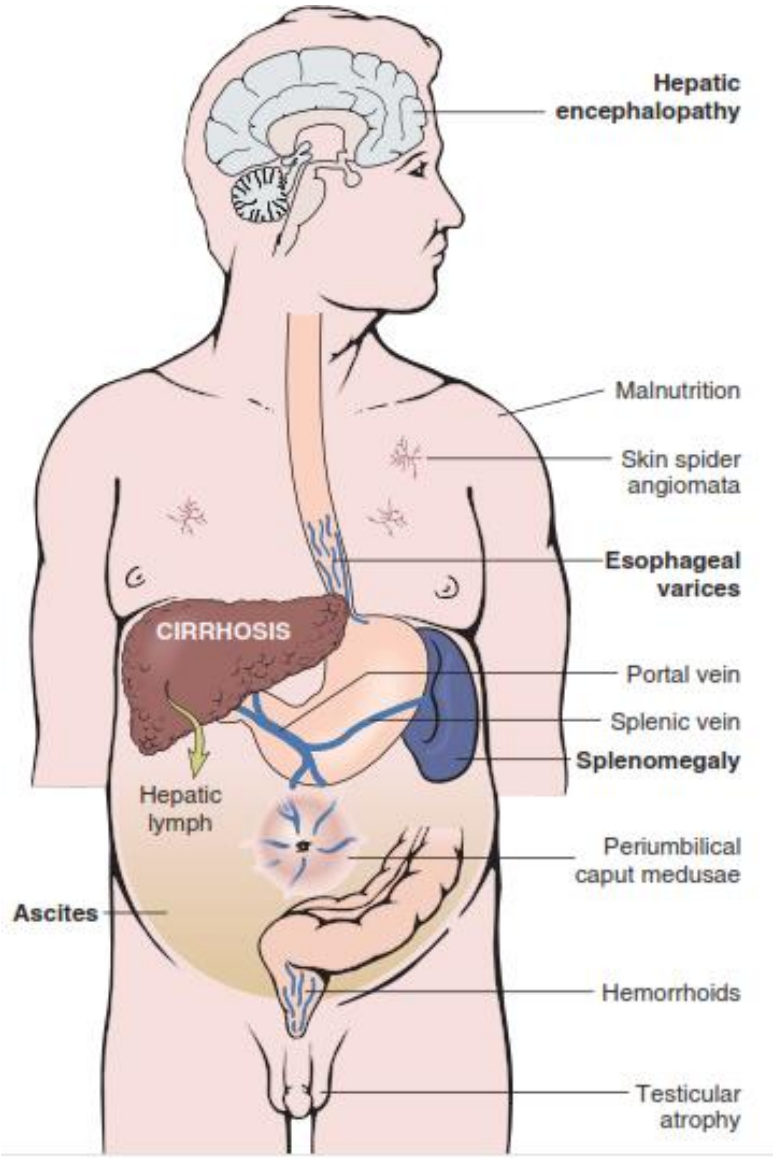
CLINICAL FEATURES OF CIRRHOSIS:

- Fatigue
- Anorexia
- Weight loss
- Jaundice
- Digital Clubbing, hypertrophic osteoarthropathy
- White nails[10]
- Palmar erythema[11]
- Spider naevi[12]
- Gynaecomatia
- Hypogonadism – testicular atrophy, loss of libido
- Parotid enlargement – in alcoholics[15]
- Dupuytren's contracture[13]
- Foetor hepaticus[14]
- Ascites

- Peripheral edema
- Gastrointestinal bleeding
- Sleep disturbances
- Altered sensorium
- Asterixis
- Splenomegaly

Figure 4: Palmar erythema

Figure 5: Clinical presentation of cirrhosis



LABORATORY FINDINGS IN CIRRHOSIS:

- Liver enzymes:[16]
    - Moderate elevation of alanine aminotransferase (ALT) & aspartate aminotransferase (AST)
    - Elevated alkaline phosphatase – more common in primary biliary cirrhosis & primary sclerosing cholangitis.
    - Elevated Gamma-glutamyl transpeptidase (GGT) – alcohol induced chronic liver disease.
- Normal Bilirubin in well compensated cirrhosis.
- Prolonged Prothrombin time
- Decreased serum Albumin
- Increased Globulins
- Reversal of albumin-globulin ratio
- Hyponatremia – correlates with disease severity
- Hematologic[17]
    - Coagulopathy
    - Thrombocytopenia
    - Leukopenia
    - Anemia

Ultrasonagraphy of abdomen:[18,19]

- Non-invasive test.
- Small shrunken liver
- Nodular surface
- Increased liver echoes.

Fibroscan – to assess the severity of liver fibrosis in cirrhosis.

Liver biopsy [20]– the confirmatory test, sensitivity 80-100%

PROGNOSTIC SCORES FOR CIRRHOSIS:

- Child Turcotte Pugh classification (CPC)
- Model for End stage Liver Disease (MELD)

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
Clinical and Lab Criteria	Points*		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
International normalized ratio	<1.7	1.7-2.3	>2.3
*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)			
Class A = 5 to 6 points (least severe liver disease)			
Class B = 7 to 9 points (moderately severe liver disease)			
Class C = 10 to 15 points (most severe liver disease)			

Model for End stage Liver Disease SCORE

$$\textbf{MELD} = 3.78 \times \log_e \text{serum bilirubin (mg/dL)} + 11.20 \times \log_e \text{INR} + 9.57 \times \log_e \text{serum creatinine (mg/dL)} + 6.43 \text{ (constant for liver disease etiology)}$$

Ranges between 6 and 40.

COMPLICATIONS OF CIRRHOSIS:

1) Portal hypertension Gastro esophageal varices Portal hypertensive gastropathy Ascites Splenomegaly, Hypersplenism Spontaneous bacterial peritonitis 2) Hepatorenal syndrome Type I Type II 3) Hepatic encephalopathy 4) Hepatopulmonary syndrome 5) Portopulmonary syndrome 6) Malnutrition	7) Coagulopathy Factor deficiency Fibrinolysis Thrombocytopenia 8) Bone disease Osteopenia Osteomalacia Osteoporosis 9) Haematological abnormalities Anemia Neutropenia Thrombocytopenia Hemolysis

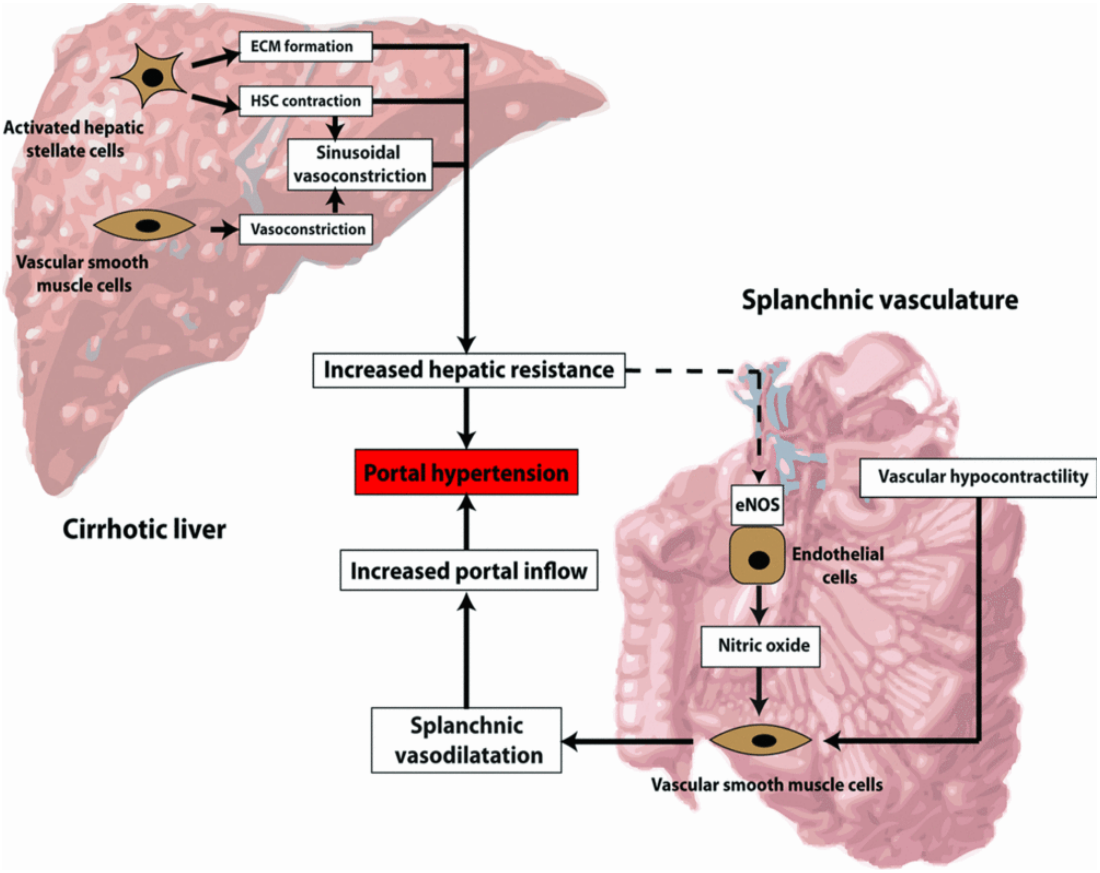
PORTAL HYPERTENSION:

Hepatic venous pressure gradient (HVPG) >5 mm Hg → indicates portal hypertension.[8]

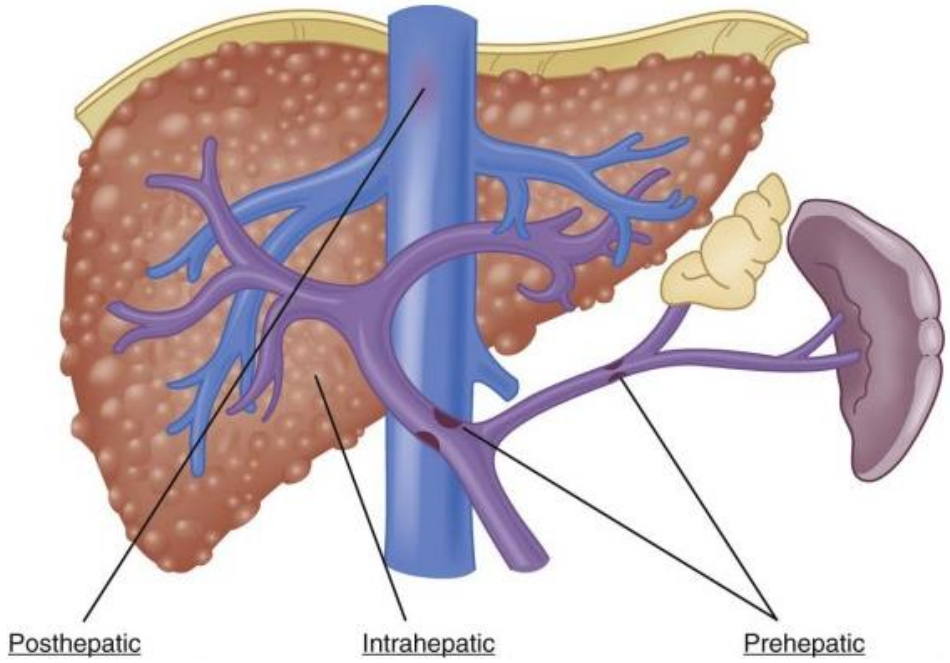
It is caused by

- Increased intrahepatic resistance to blood flow.
- Increased splanchnic blood flow.

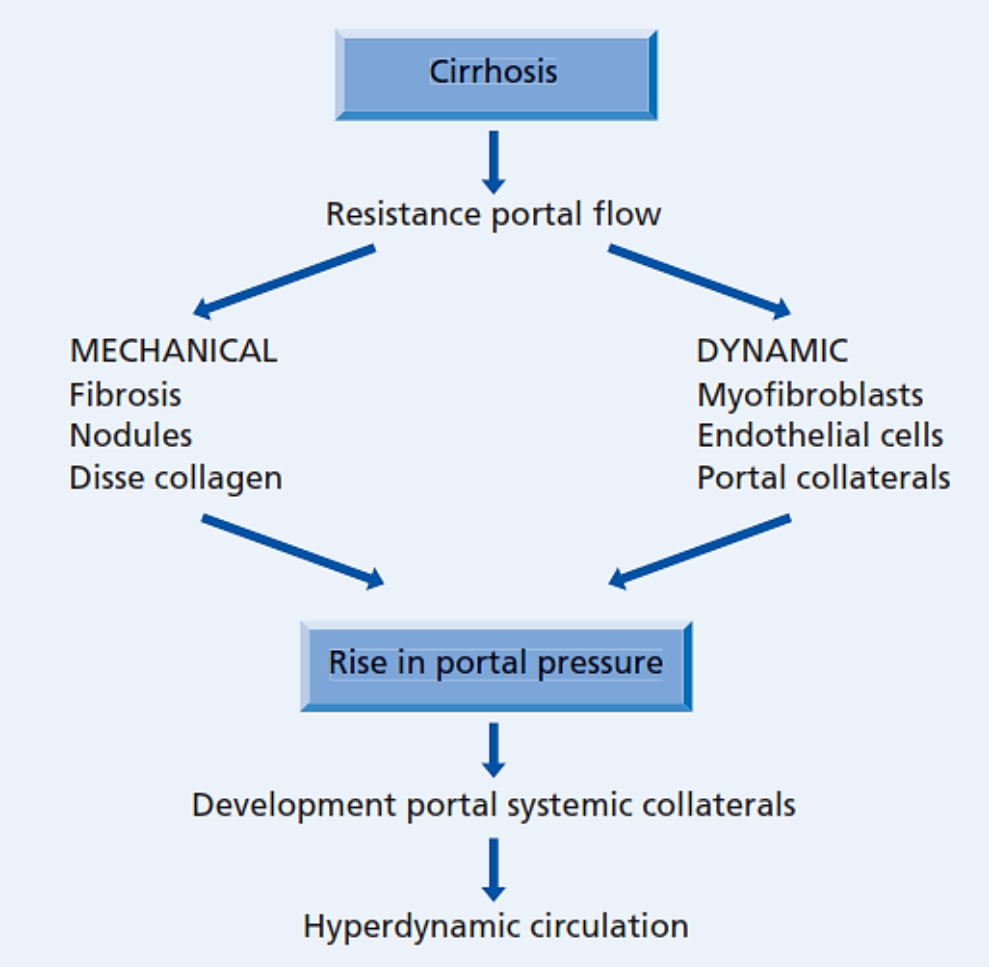
Figure 6: Pathogenesis of Portal hypertension



CLASSIFICATION OF PORTAL HYPERTENSION:



1.Prehepatic
Portal vein thrombosis – independent of cause, splenic vein thrombosis, cavernous transformation of the portal vein, splenic arteriovenous fistula, idiopathic tropical splenomegaly
2.Intrahepatic
a) presinusoidal
Schistosomiasis, chronic viral hepatitis HBV, HCV, cirrhosis biliaris primaria, myeloproliferative diseases, focal nodular hyperplasia, idiopathic portal hypertension, sarcoidosis, tuberculosis, Wilson's disease, hemochromatosis, amyloidosis, remaining storing diseases, polycystic liver disease, infiltration of liver hilus - independent of cause, benign and malignant neoplasms
b) sinusoidal
Liver cirrhosis - independent of etiology, acute viral and alcoholic hepatitis, acute fatty liver of pregnancy
c) postsinusoidal
Venous-occlusion disease, alcoholic hyaline sclerosis of central veins
3.Extrahepatic
Hepatic veins thrombosis (Budd- Chiari disease), inflammatory/neoplastic infiltration cavering hepatic veins, caval inferior occlusion (thrombosis, neoplasms), cardiac diseases: chronic right ventricular failure, chronic constrictive pericarditis, tricuspid insufficiency



Clinical features:

- Upper gastrointestinal bleeding due to varices,
- Ascites & peripheral edema
- Splenomegaly
- Reduced platelets and leukocytes.

Treatment:

Aimed at

- Reducing portal blood flow
- Decreasing intrahepatic resistance

Drugs decreasing Portal venous blood flow:

- Nonselective β-blockers – propranolol, nadolol
- Vasopressin
- Somatostatin & octreotide

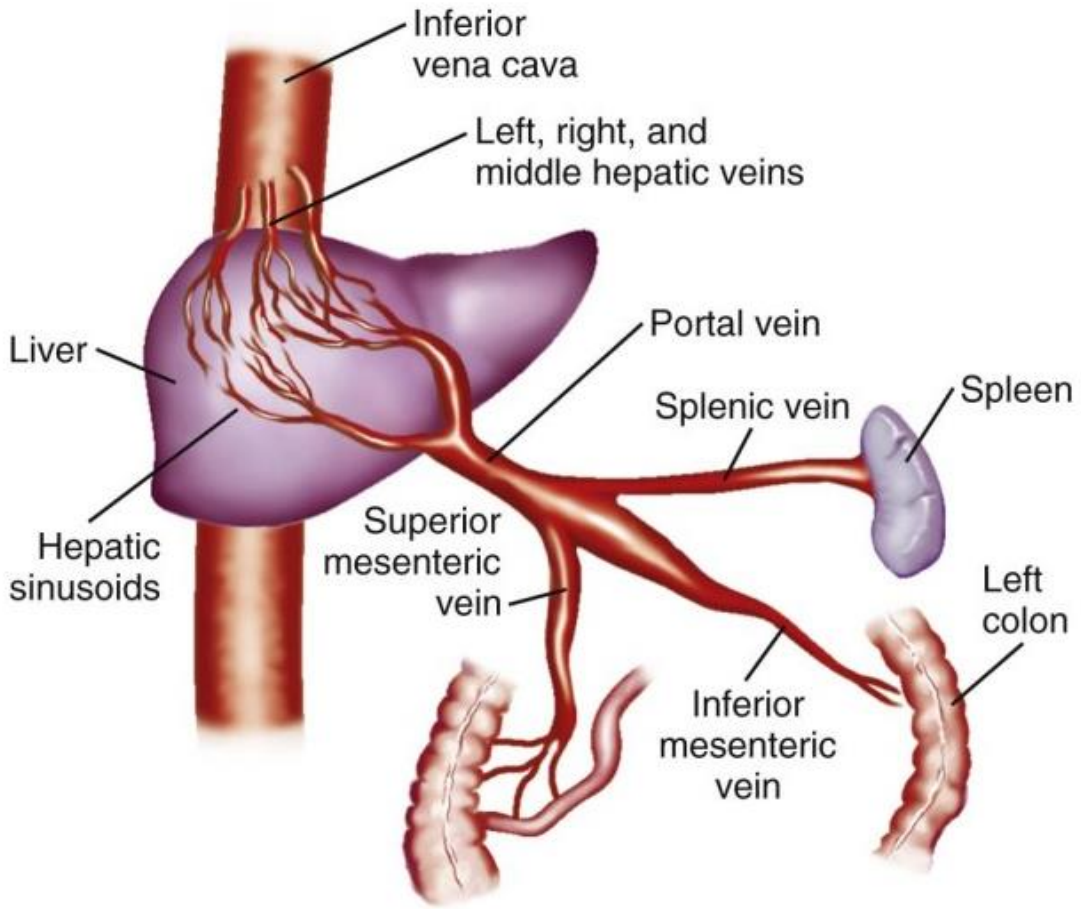
Drugs reducing Intrahepatic Resistance:

- α1-Adrenergic blockers – prazosin
- Angiotensin receptor blockers (ARBs) – losartan
- Nitrates

Endoscopic therapy for varices.

Shunt procedures – TIPS

Figure 7: Anatomy of portal circulation



VARICEAL HEMORRHAGE:

Bleeding from varices occurs due to increased portal pressure. It is dreadful complication.

Increased portal pressure → portosystemic collaterals → dilate varices, walls become thinner.

Any further increase in variceal pressure / size → rupture & clinical hemorrhage

Gastroesophageal varices – most common source of upper gastrointestinal bleed in cirrhotic patients.

Incidence 5–15% / per year.[5]

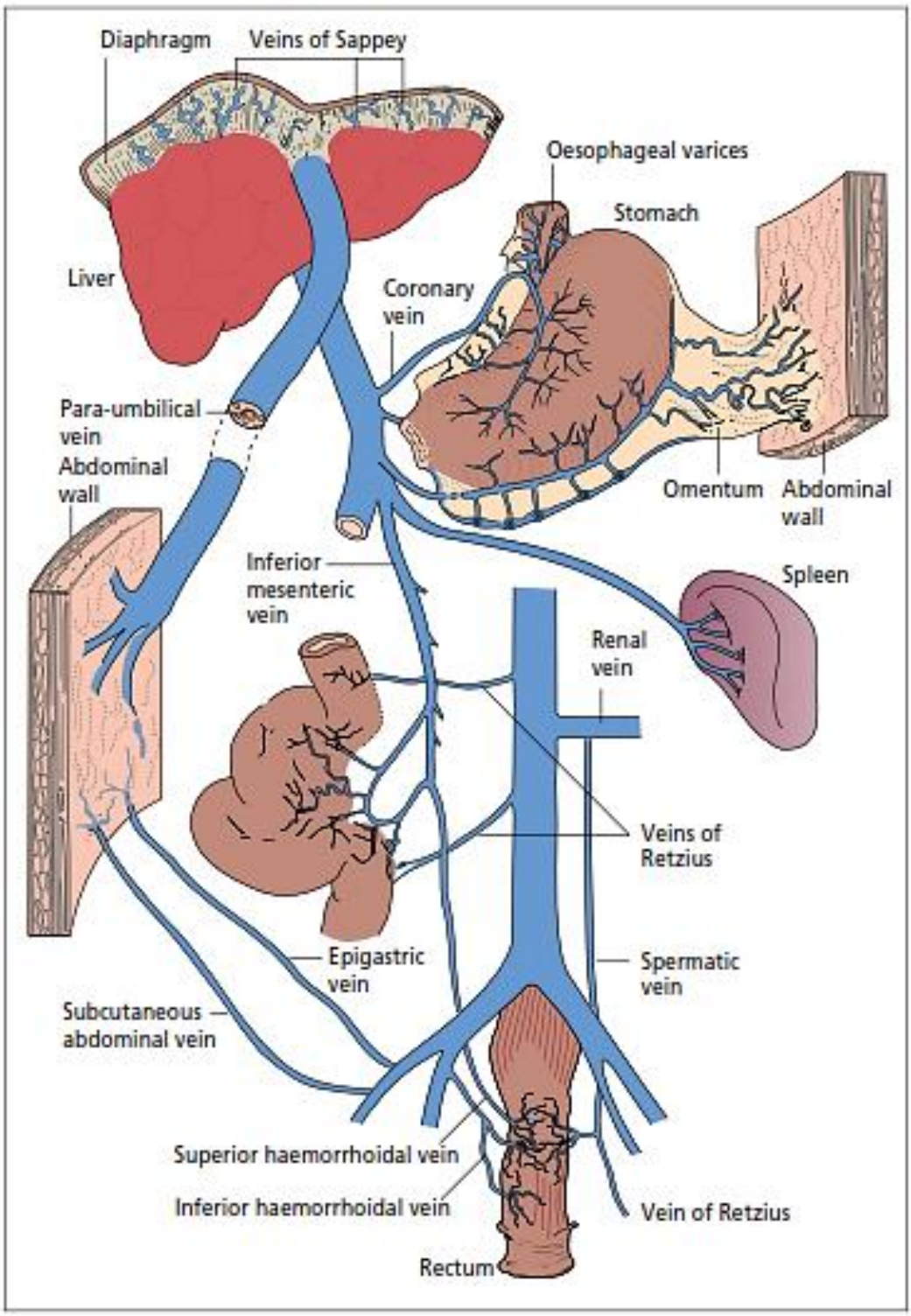
Bleeding from varices occurs in one third of cirrhotics

Caput medusa – prominent veins radiating from umblicus

Sites of portal-systemic anastomosis in cirrhosis:

Retroperitoneum: *Portal*: Colonic veins *Systemic*: Body wall veins
Lower esophagus: *Portal*: Left gastric veins *Systemic*: Azygos veins
Bare area of liver: *Portal*: Portal veins *Systemic*: Inferior phrenic veins
Umbilicus: *Portal*: Veins of ligamentum teres *Systemic*: Superior and inferior epigastric veins
Upper anal canal: *Portal*: Superior rectal vein *Systemic*: Middle and inferior rectal veins

Figure 8: Sites of portal-systemic anastomosis in cirrhosis[21]



Endoscopy

Varices are identified by endoscopy.

- Upper GI endoscopy → gastroesophageal varices
- Sigmoidoscopy → rectal varices

Varices are graded by endoscopy in to 3 types

- Grade I
- Grade II
- Grade III

Figure 9: Endoscopic Grading of varices

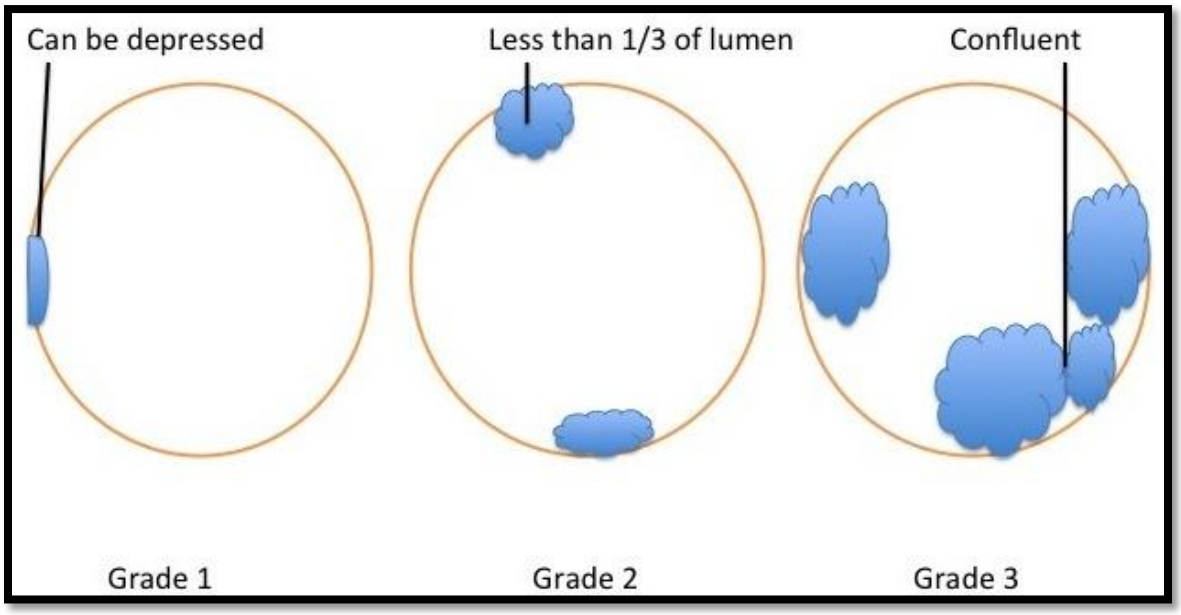


Figure 10: Upper GI endoscopy showing esophageal varices

Portal hypertensive gastropathy – in fundus of stomach, mosaic-like pattern

Factors predicting the risk of bleeding:[5]

- Severity of cirrhosis (Child's class, MELD score)
- Height of hepatic vein wedge vein pressure
- Location & size of varices
- Endoscopic findings – cherry red spots, red wale signs, erythema

Treatment of variceal hemorrhage due to portal hypertension include

- Acute variceal hemorrhage – resuscitation, vasoconstricting agents like somatostatin or octreotide, emergency endoscopic sclerotherapy or band ligation

- Primary prophylaxis – non selective beta blockers or endoscopic variceal band ligation
- Prevention of re-bleeding after an initial variceal bleed – beta blockade, portosystemic shunt surgery (TIPS)

ASCITES:

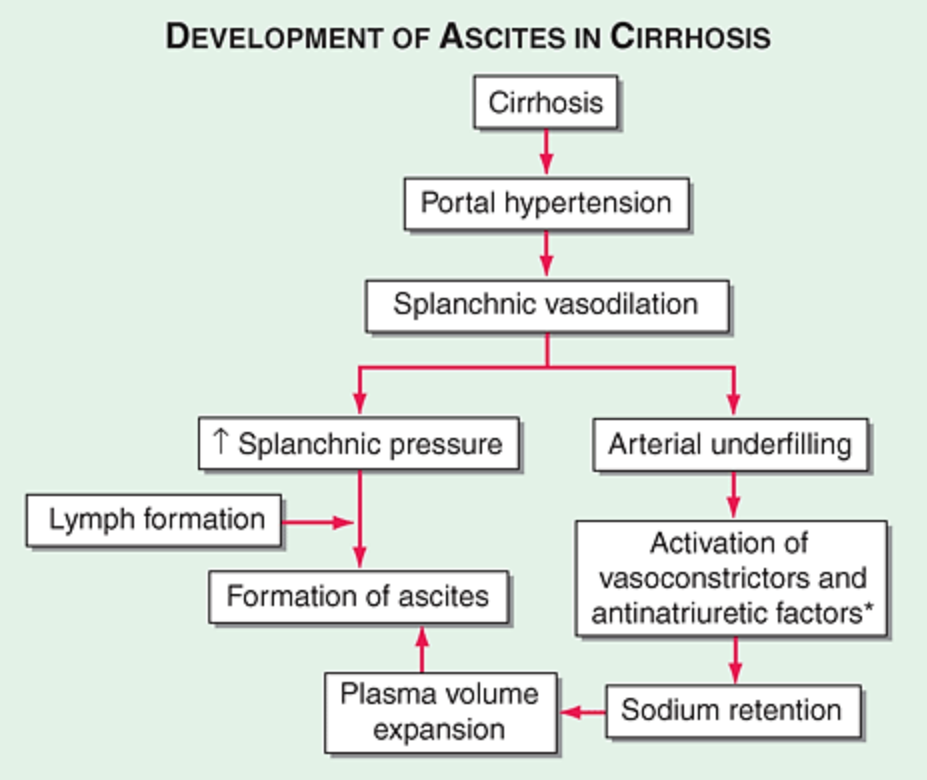
Ascites - accumulation of free fluid in the peritoneal cavity.

Portal hypertension is the common cause for ascites.

Malignant or infectious causes can be present as well.

Pathogenesis:[5]

- Increase in portal pressure & vasodilation of the splanchnic arterial system → increase in portal venous inflow & increased production of splanchnic lymph. Vasodilating factors (nitric oxide) are responsible for vasodilatory effects.
- Activation of renin-angiotensin-aldosterone system and hyperaldosteronism leads to retension of sodium causing fluid accumulation & expansion of ECF volume. This results in peripheral edema and ascites



- Hypoalbuminemia (due to reduced synthesis from liver) & reduced plasma oncotic pressure → fluid loss from vascular compartment into peritoneal cavity.
- Ascites develops insidiously. Patients usually have 1-2 litres of fluid in the abdomen before they are aware that there is an increase.
- Massive ascites → compromise respiratory function, dyspnoea occurs.
- Hepatic hydrothorax also contributes to respiratory symptoms. It is common on right side. Free flow of fluid into the thoracic cavity occurs through a diaphragmatic rent.

SBP – SPONTANEOUS BACTERIAL PERITONITIS

- Spontaneous infection of ascitic fluid without intraabdominal source.
- Occur in up to 30% of individuals
- 25% in-hospitality mortality rate.
- Most common organisms – Escherichia coli & other gut bacteria.
- Diagnosis criteria - ascitic fluid absolute neutrophil count >250 cells/µL.

HEPATORENAL SYNDROME (HRS):

Functional renal failure with no obvious renal pathology.

Incidence 10% in advanced cirrhosis / acute liver failure.

- Type I HRS – progressive impairment in kidney function with significant reduction in creatinine clearance within 1-2 weeks.
- Type II HRS – reduction in GFR with an elevation of serum creatinine level, but it is fairly stable, better outcome than type I HRS.

HEPATIC ENCHEPHALOPATHY:

Hepatic encephalopathy (HE) – transient & reversible neurologic & psychiatric manifestations in the setting of heaptic failure.[22]

Occurs in 50-70% of cirrhotics

Poor prognostic indicator

Without liver transplantation in HE – survival rates 42% & 23% respectively in 1st and 3rd year

Symptoms - mild mental disturbances to coma.

Triggered by a precipitating event resulting in raised level of ammonia.

Precipitating events

- Infections
- Increased protein load
- Gastrointestinal bleeding
- Electrolyte disturbances - hypokalemia

Intra & extrahepatic shunting of portal blood into systemic circulation → toxic substances not detoxified by liver → metabolic abnormalities in the central nervous system.

Treatment:

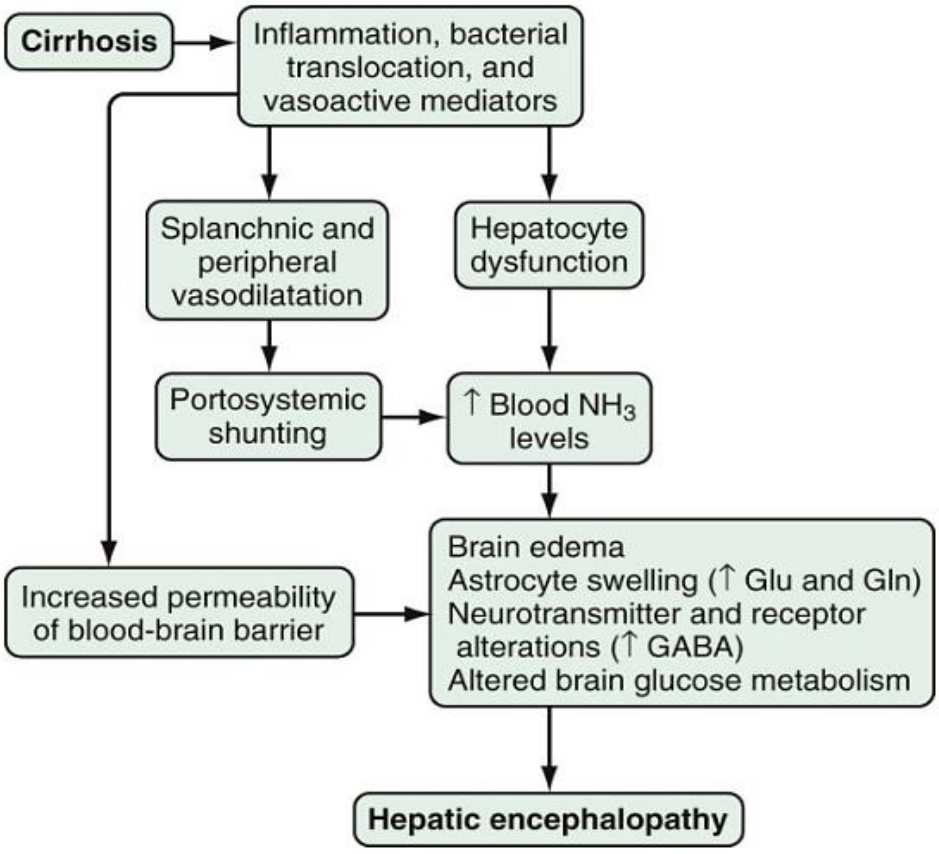
Avoiding precipitating events

Reduction of elevated serum ammonia production

Disaccharides (non absorbable) – lactulose

L-ornithine L-aspartate, Zinc, Flumazenil

Transplantation of liver



COAGULOPATHY:

Coagulopathy common in cirrhotic patients.

Decreased clotting factor synthesis.

Impaired clearance of anticoagulants.

Hypersplenism due to portal hypetension → Thrombocytopenia

CARDIOVASCULAR CHANGES IN CIRRHOSIS:

Hyperdynamic circulation occurs in cirrhosis

Decreased peripheral vascular resistance, decreased arterial BP and increased cardiac output.

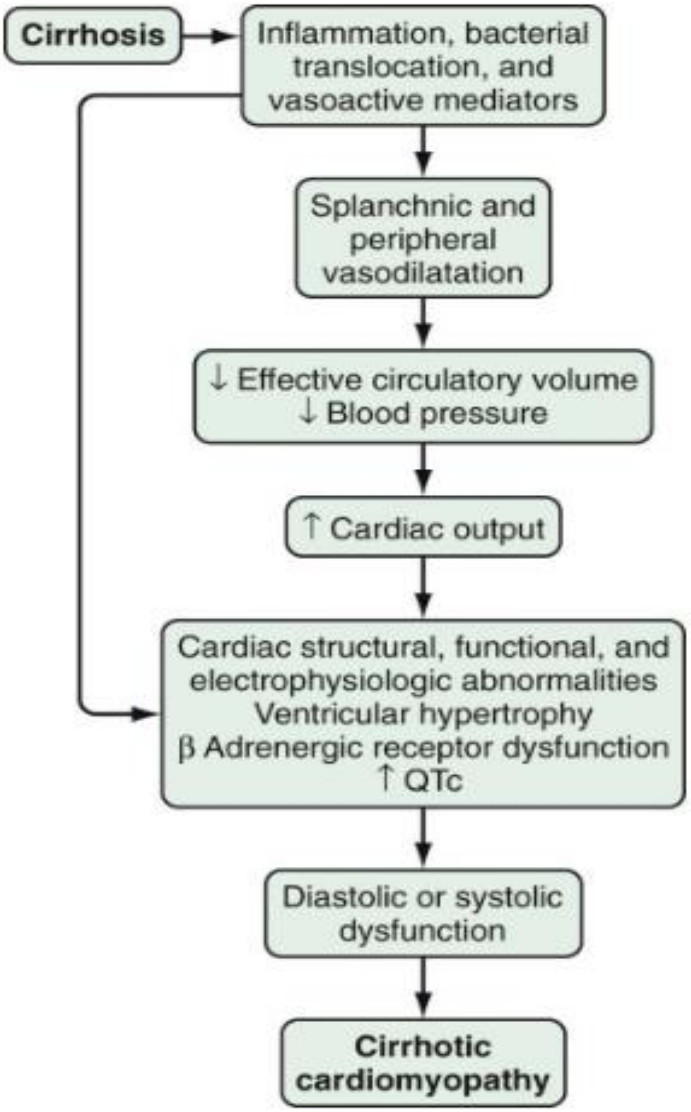
Kowalski et al[23] were the first to report that cirrhotic patients had abnormal cardiovascular changes and a prolonged QTc.

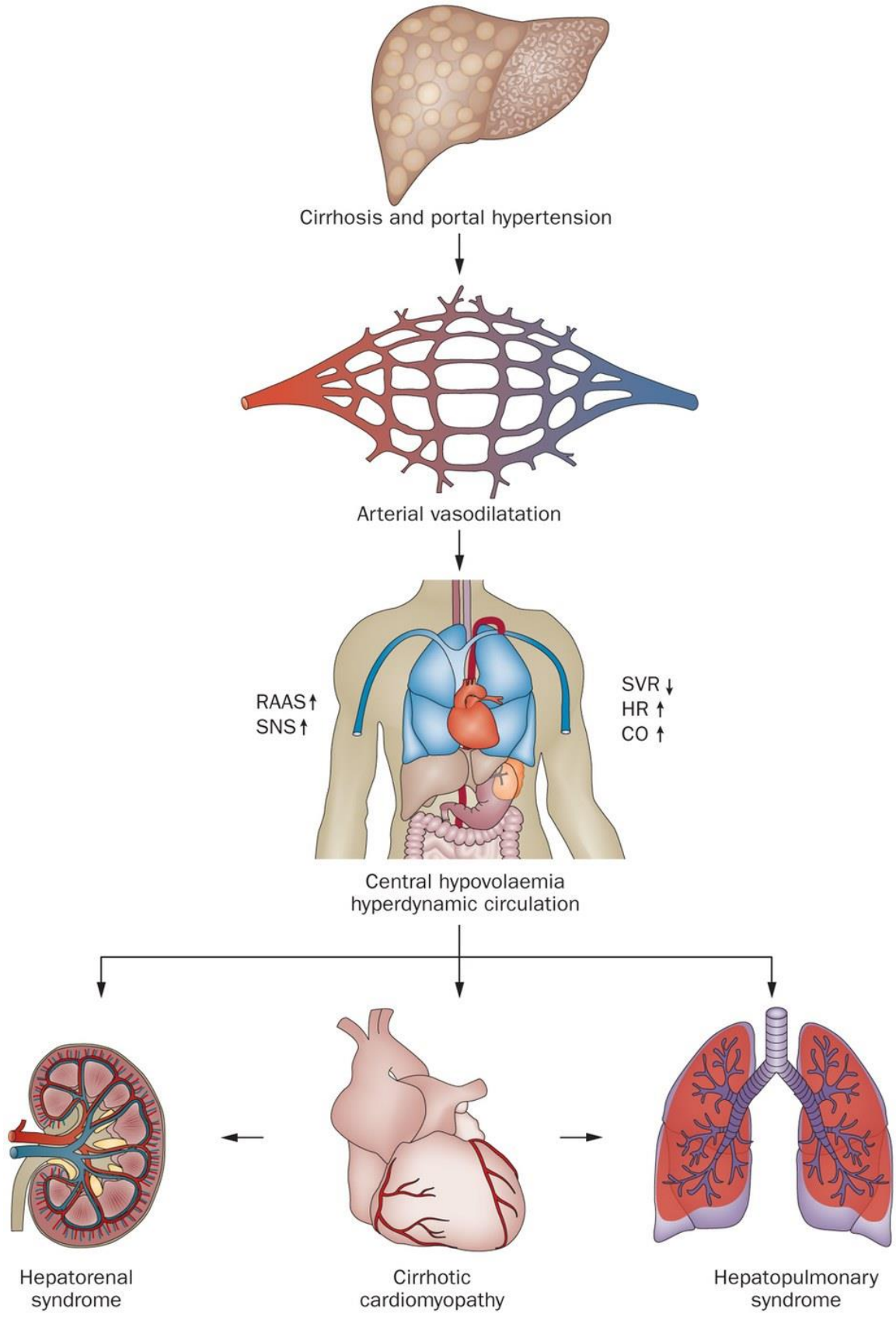
Cirrhotic cardiomyopathy is characterized by

- Systolic dysfunction
    - Resting ejection fraction <55%
    - With exercise, volume change or pharmacological stress → blunted increase in cardiac output

- Diastolic dysfunction
    - E/A ratio < 1.0
    - Prolonged isovolumetric relaxation time & deceleration time
- Electrophysiological changes

Mechanism of cirrhotic caridiomyopathy




Cirrhosis and portal hypertension
Arterial vasodilatation
RAAS↑
SNS↑
SVR↓
HR↑
CO↑
Central hypovolaemia
hyperdynamic circulation
Hepatorenal syndrome
Cirrhotic cardiomyopathy
Hepatopulmonary syndrome

PULMONARY MANIFESTATIONS IN CIRRHOSIS

Pulmonary complications of Cirrhosis can affect the lung parenchyma, pulmonary circulation and the pleura. Pulmonary manifestations in cirrhosis can present as follows,

- Hepato-pulmonary syndrome (HPS)
- Hepatic hydrothorax
- Porto-pulmonary hypertension (PPH)

The most common clinical features are Dyspnea and hypoxemia.

HEPATOPULMONARY SYNDROME:

Hepatopulmonary Syndrome (HPS) is characterized by[23]

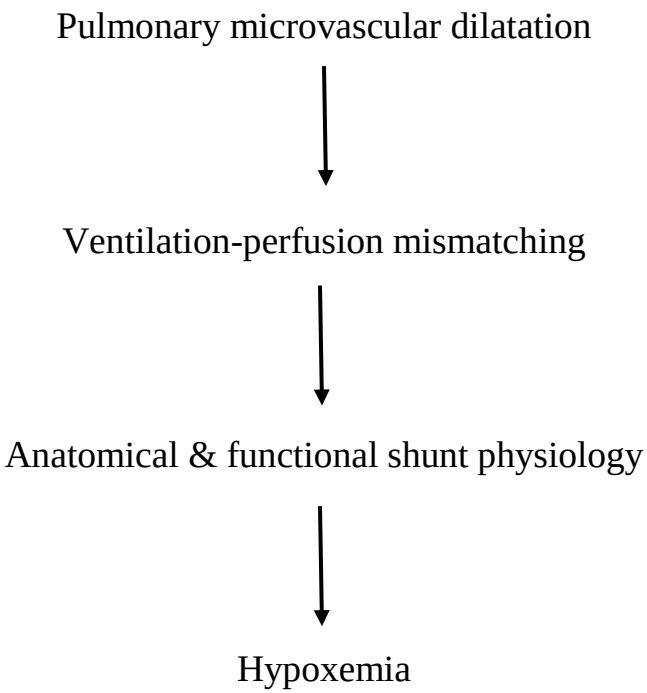
- Liver diasease
- Hypoxemia
- Pulmonary microvascular dilatation

Liver-lung relationship was first noted in 1884 by Fluckiger.[3] But this was not formalized at that time. In 1997 Kennedy & Knudson explained HPS as a disease presenting with hypoxemia and intrapulmonary vascular dilatations.[4]

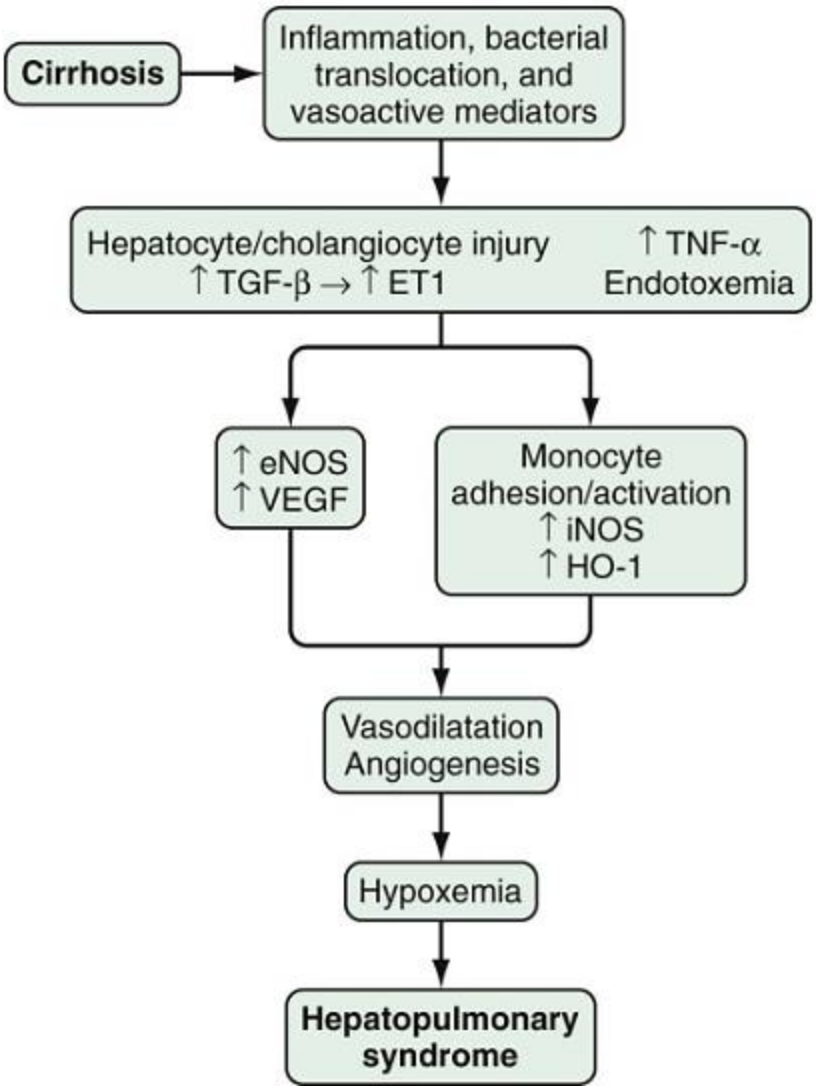
About 4% to 19% prevalence rate of HPS.[2] Most cases have occurred in patients with cirrhosis & portal hypertension. Due to different cut-off values (in various studies) for defining arterial hypoxemia there is disparity in the prevalence rate of HPS.

PATHOPHYSIOLOGY:

Pathological hallmark – dilatation of pulmonary microvasculature.



Functional vasodilatation was due to reduced synthesis or inadequate metabolism of vasoactive agents.

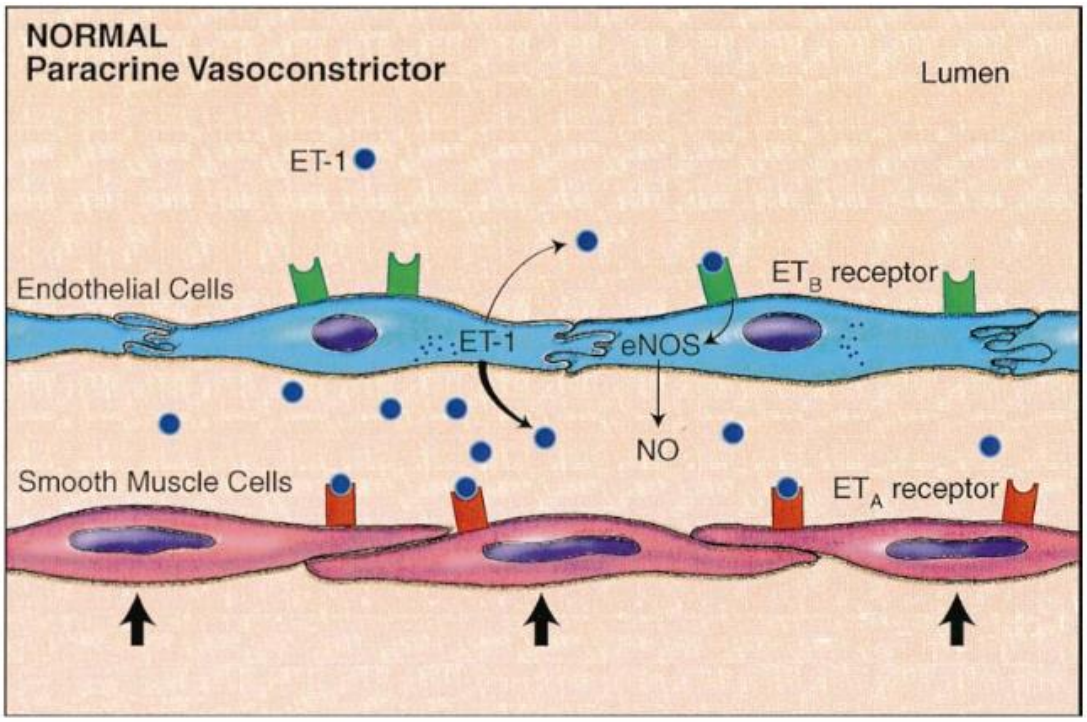


Nitric oxide (NO) is the leading vasoactive agent. There is increased production nitric oxide from the pulmonary circulation. In cirrhotic patients with HPS, there is increase in exhaled NO.[25] Both endothelial & inducible NO synthases are overexpressed in pulmonary microcirculation. N ^{G}-nitro -L arginine methyl ester (L-NAME) and Methlyene blue inhibit NO production which transiently alleviates HPS

In the normal vasculature, endothelin-1 (ET-1), produced locally in endothelial cells, acts as a paracrine vasoconstrictor through activation of the endothelin A (ET) receptor on smooth muscle cells. To a lesser extent, luminal release of ET-1 stimulates nitric oxide (NO) production by endothelial nitric oxide synthase (eNOS) through activation of the endothelin B (ET A) receptor on endothelial cells.[26]

In HPS, ET-1 reaches the lung through the pulmonary circulation and acts as an endocrine vasodilator by stimulating the ET receptor on the luminal surface of the endothelial cell and preferentially increasing NO production. This is depicted in the following diagram

Figure 11: Effect of Endothelin-1 in the normal and HPS pulmonary microvasculature



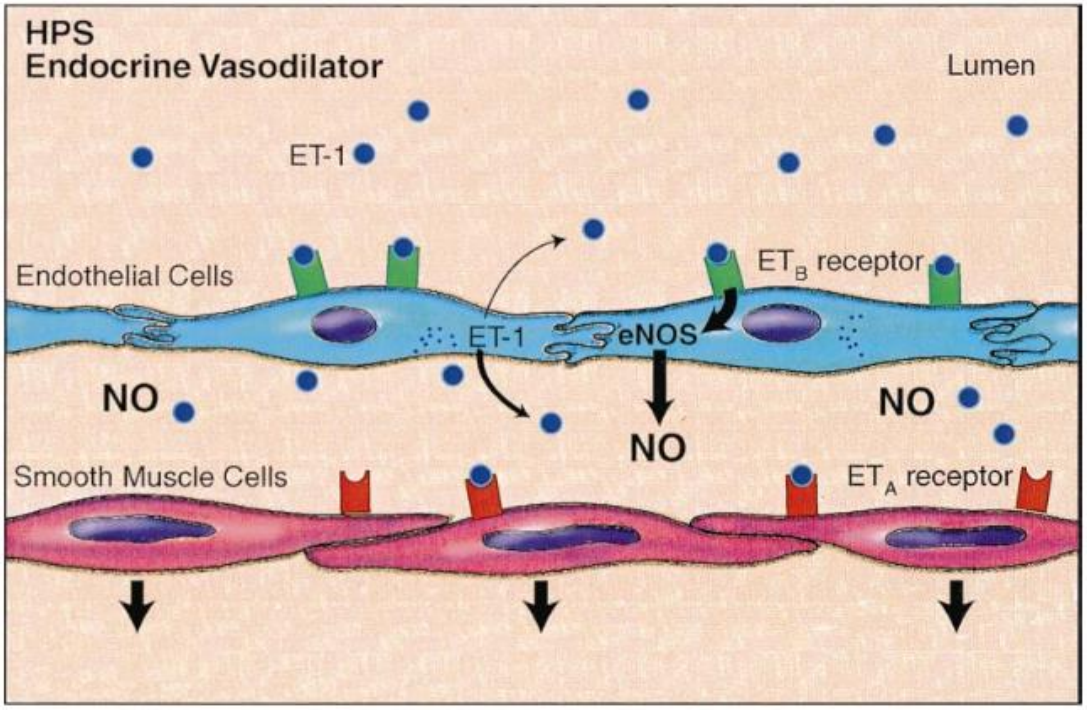
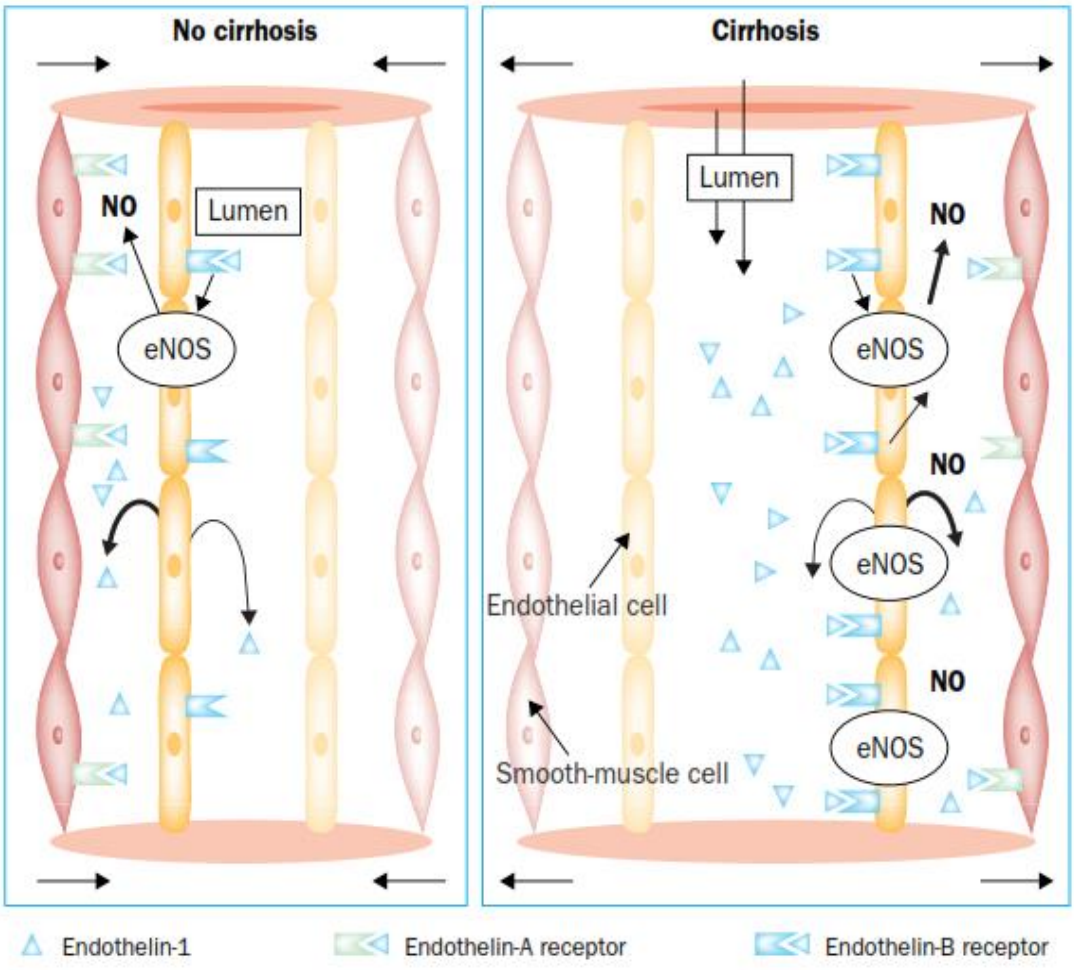


Figure 12: Hypothesis in intrapulmonary dilatation in hepatopulmonary syndrome



MECHANISM OF HYPOXEMIA:[83]

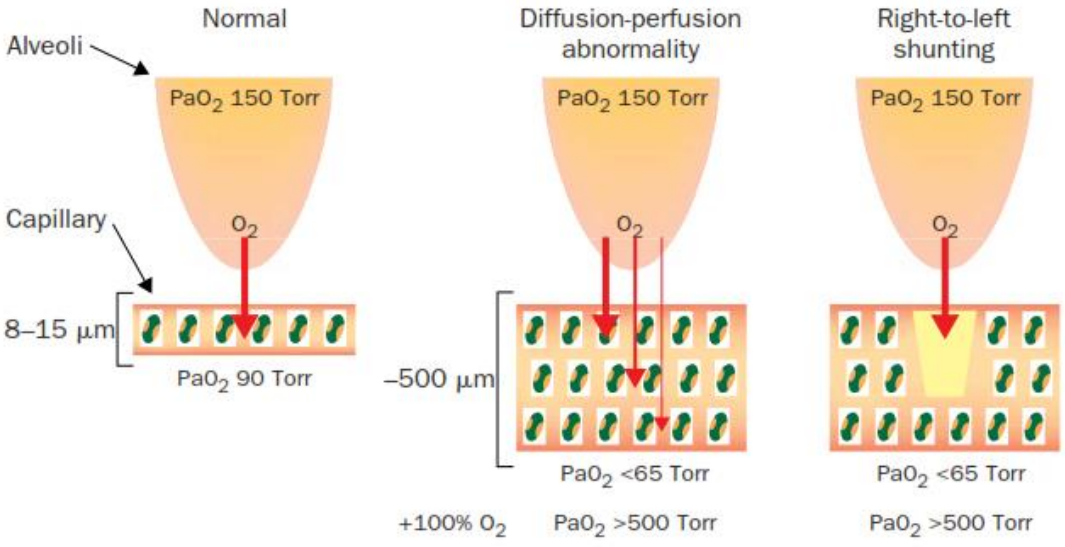
- Abnormal Diffusion
- Ventilation perfusion (V/Q) mismatch

Significant improvement in arterial oxygenation is observed in patients of HPS who are given 100% oxygen.[27] This supports the finding that the VA/Q mismatch is a predominant cause of hypoxemia in HPS.[28]

Hypoxemia is also caused by a ‘‘diffusion-perfusion defect’’.[29] Pulmonary blood flow is increased to such an extent in patients with liver disease that there is insufficient time for adequate exchange of oxygen at the capillary–alveolar interface.

In support of this theory, investigators have found a correlation between impairments in oxygenation and the transit time for blood flow through pulmonary circulation in patients who have liver disease but who do not have hypoxemia.[24]

Figure 13: Pathophysiology of hypoxemia in HPS



Arterial oxygenation is influenced by position in all patients, but this effect is accentuated in patients who have HPS.[30] Under normal circumstances arterial oxygenation falls in the supine position. It is due to gravity which pushes the abdominal contents into the diaphragm, reducing functional residual capacity and causes venous admixture as a result of impaired VA/Q mismatching.[31,84] Oxygen desaturation in the supine position is often enhanced in patients who have liver disease. This is because of the added effects of ascites and increased intrathoracic blood volume on functional residual capacity.

In contrast, patients with HPS often experience orthodeoxia and platypnea, deoxygenation and dyspnea in standing & sitting positions when compared to supine position. These are due to redirection of pulmonary blood flow in upright posture, to dilated vessels in lung bases.[32]

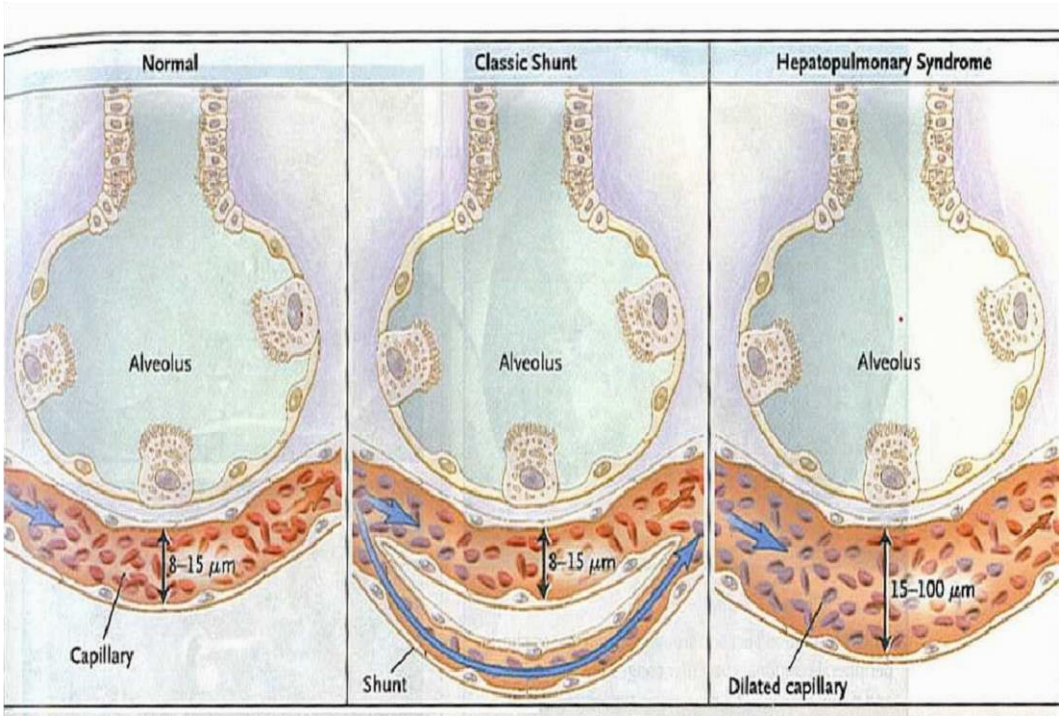
Orthodeoxia is a unique observation that can be used to confirm a diagnosis of HPS.[1] A fall in oxygen saturation upon assuming the standing position has been observed in patients who have mild liver disease who do not suffer from oxygen desaturation and therefore do not have HPS.[33] The latter observation indicates that the diagnostic and prognostic value of orthodeoxia is an independent observation that needs further clarification.

In normal lung → oxygen diffuses rapidly into the capillary (8-15 µm)

In anatomical shunt, blood bypasses the alveolus.

In HPS → oxygen unable to diffuse into the center of dilated capillary (15-100 µm) → hypoxia occurs.

Figure 14: Intrapulmonary dilatation in HPS

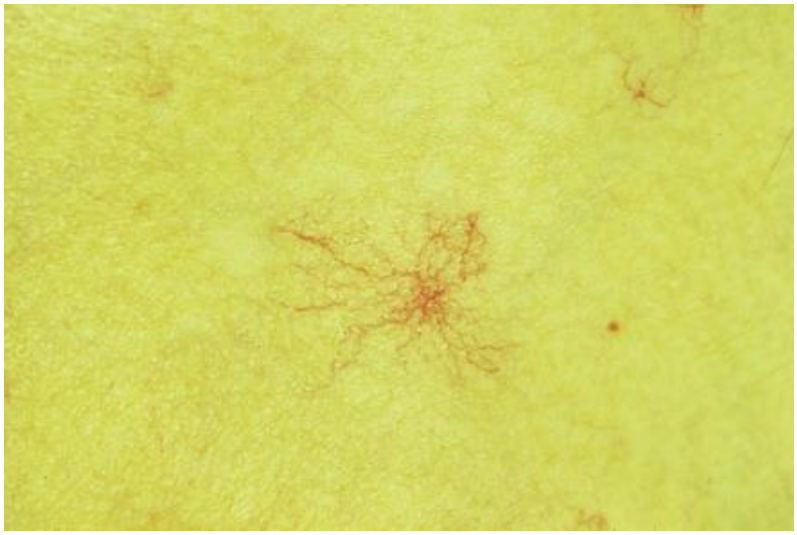


CLINICAL FEATURES:

The clinical course of HPS is poorly defined. Acute development (days to weeks) of the syndrome appears unlikely. High suspicion is needed to diagnosis HPS. Clinical features of HPS include

- Dyspnoea – insidious onset, most common feature[34]
- Platypnoea
- Orthodeoxia
- Cyanosis
- Digital Clubbing
- Spider angioma[82]

Figure 15:Spider naevi



Progressive worsening of hypoxemia over months to years has been reported with an approximate mortality of 41% 2.5 years from diagnosis.[38] Comorbid conditions (infection/sepsis) can result in acute and dramatic respiratory deterioration.

Orthodeoxia:[35,86]

- Accentuation of hypoxemia in upright position compared to supine position
- Fall in PaO_2 ≥5%
- Fall in PaO2 ≥4 mm Hg
- Mechanism – In upright posture → more perfusion in lung bases → greater functional shunting
- Highly specific for HPS.

Alizadeh et al (2006)[36] conducted a study in which

- Dyspnea - presenting feature in HPS
- Cyanosis - seen in 90% of cases.

Significant relationship exist between spider angioma and vasodilatation of pulmonary bed.[37] Hence spider nevi can be a cutaneous marker in patients with intrapulmonary dilatations.

DISEASE SEVERITY:

HPS can be graded according to the degree of hypoxemia

Classification ERS Task Force[17]	Arterial oxygen tension (PaO_2)
Very severe	<50 mmHg
Severe	≥50 PaO_2 <60 mmHg
Moderate	≥60 PaO_2 <80 mmHg

DIAGNOSIS OF HPS:

HPS can be diagnosed by

- Arterial blood gas analysis
- Echocardiography with contrast
- Lung perfusion scanning
- CT pulmonary angiography
- High resolution CT

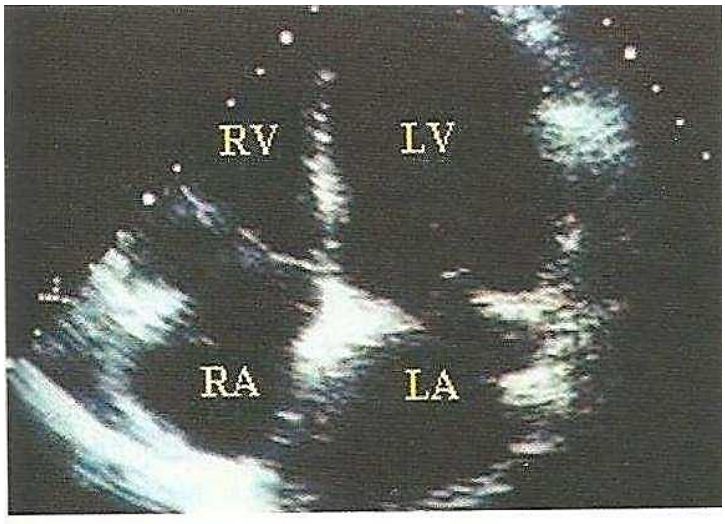
2D transthoracic contrast echocardiogram:[85]

The most sensitive & most common technique employed

Saline is used as contrast agent – produces microbubbles on echo

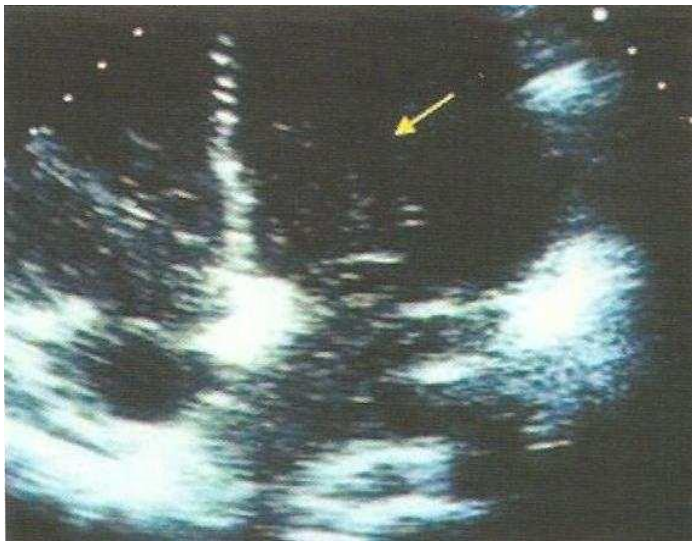
Positive test – visualization of microbubbles in left cardiac chambers after 3 cardiac cycles[39,40]

Figure 16: Contrast echocardiogram to detect intrapulmonary vasodilatation



Echocardiogram before contrast.

Echo after saline contrast: Right atrium and Right ventricle showing microbubbles



Positive contrast test in HPS: Visualization of microbubbles in left atrium (arrow) and left ventricle (3 cardiac cycles later)

Echocardiogram can also assess

- Cardiac dysfunction
- Pulmonary arterial pressure – pulmonary hypertension

Contrast echo more sensitive than lung perfusion scan[78]

Lung perfusion scanning:

- Radionucleotide used – Technetium-99m-labelled macro aggregated albumin particles (^{99m}TcMAA scan)
- Macro aggregated albumin particles (50-100 micrometer) – injected IV.

- Normally all particles are trapped within the pulmonary vasculature.
- In HPS patients, some particles pass through dilated pulmonary capillaries and lodge in various systemic arterial bed.
- Shunt fraction calculated from quantitative imaging of lung & brain.[41]
- Shunt fraction > 6% → significant

Advantage: Specific for detection of HPS even in the presence of co-existing intrinsic pulmonary disease

Lung perfusion scanning less sensitive than contrast echo.[42]

Figure 17: Lung perfusion scan in HPS: radionucleotide detected in kidneys

Pulmonary angiography:

Two angiographic patterns are seen[43]

Type I	Diffuse, normal vessels or fine diffuse spidery vascular abnormalities
Type II	Focal, more infrequent, similar focal arteriovenous communications

High resolution CT:

Detect dilated pulmonary vessels[44]

Degree of dilatation observed can be correlated with the severity of gas exchange

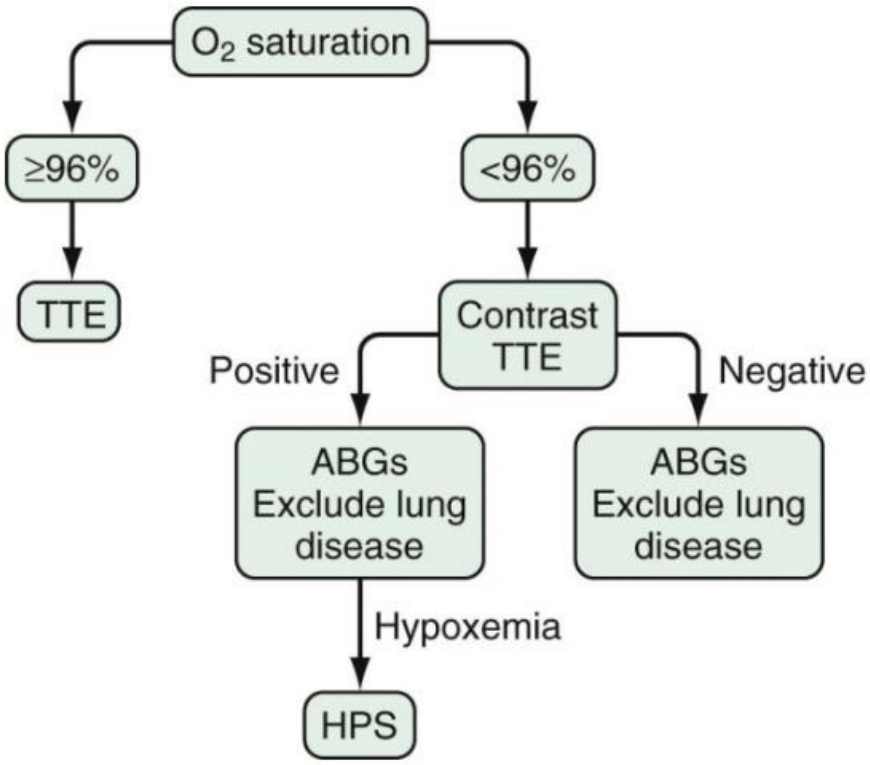
SCREENING OF HPS:

Screening for HPS is important especially in patients awaiting liver transplantation. Screening tests include

- Pulse oximetry
- Arterial blood gas analysis
- Contrast echocardiogram

- Detect intrinsic cardio-pulmonay disease

Screening for HPS



NATURAL HISTORY AND PROGNOSIS:[45]

- Mortality is significant in patients with HPS and may be in part due to causes directly related to intra pulmonary vasodilatation.
- The prognosis of HPS is poor in cirrhosis.
- HPS is a significant risk factor for patient's survival.
- Hepatopulmonary syndrome can occur in mild liver disease also.

- HPS is associated with increased mortality and morbidity in patients awaiting liver transplantation.
- Degree of arterial hypoxemia influence patient's survival. This was shown in a study conducted by Swanson and colleagues in 2005 in which survival is worse in patient group with decreased $PaO_{2.}$
- Causes of death – secondary to complications of liver dysfunction & portal hypertension, correlates with degree of hypoxemia.

MANAGEMENT OF HPS:

Medical treatment:

Following drugs were tried in HPS

- Garlic preparations[80]
- Pentoxifylline[49,50] – TNF alpha inhibitor
- Methylene blue[53,87] & inhaled N (G)-nitro-L-arginine methyl ester[54] – direct inhibition of nitric oxide
- Somatostatin
- Indomethacin[79]
- Steroids
- N-acetylcysteine

- Almitrine bimesylate[51,52]
- Oxygen therapy
- Iloprost[56]

Intervention Radiological therapy:

- Transjugular intrahepatic portosystemic shunt (TIPS)[46,47,48] – control portal pressure
- Embolotherapy[88,89] with Yttrium-90 glass microspheres[55] – eliminate intrapulmonary shunts

Liver transplantation:[90]

- Only proven treatment for HPS.
- After liver transplantation complete resolution of hypoxemia occurs in 85% of patients.[57]
- In some patients resolution may take more time[58] (more than a year).
- Mortality after liver transplantation is significantly high with 1-year survival rate – 71%.[59]
- Severe degree of hypoxemia & prominent intrapulmonary shunting → associated with increased mortality rate.

Complications after OLT:

- Pulmonary arterial hypertension[60]
- Cerebral embolic hemorrhage[61]
- Post-operative hypoxemia requiring prolonged ventilation[62]

Indication for orthotopic liver transplantation in HPS:[81]

- If PaO_2 → 50 – 60 mmHg
- If PaO_2 → <50 mmHg (on an individual basis)

Liver transplantation is the ideal treatment for HPS as there are no proven medical therapy.

HEPATIC HYDROTHORAX

Presence of pleural effusion without intrinsic respiratory or cardiac pathology in patients with cirrhosis.

Incidence up to 10%[63]

Movement of free fluid from peritoneal cavity in to pleural cavity through small diaphragmatic rents.

Can occur even without ascites.

Most common on right side[63] (67%)

May be bilateral (17%) or left sided 17%

Spontaneous bacterial empyema can occur[64]

Treatment:

- To decrease ascitic fluid formation
- Therapeutic aspiration (to relieve dyspnea)
- To obliterate the rent between pleura & peritoneum
- Shunt surgery (TIPS)
- Pleurodesis

Figure 18: Chest X-ray showing right pleural effusion in a cirrhotic patient

(A) CXA – PA VIEW

(B) CXR – RIGHT LATERAL VIEW

PORTOPULMONARY HYPERTENSION: (PPH)

Portopulmonary hypertension (PPH) is characterized by[65]

- Elevated mean pulmonary artery pressure (>25 mmHg at rest, >30 mm Hg with exercise
- Increased pulmonary vascular resistance (>240 dynes s/cm
- Pulmonary artery occlusion pressure (<15 mmHg)

Severity of PPH:

Severity	Mean arterial pulmonary pressure
Mild	25 – 35 mm Hg
Moderate	35 – 50 mm Hg
Severe	>50 mm Hg

Incidence of PPH in cirrhosis - 6%

PATHOGENESIS:[92,93]

Pathogenesis of PPH is not well understood

Embolic factors:

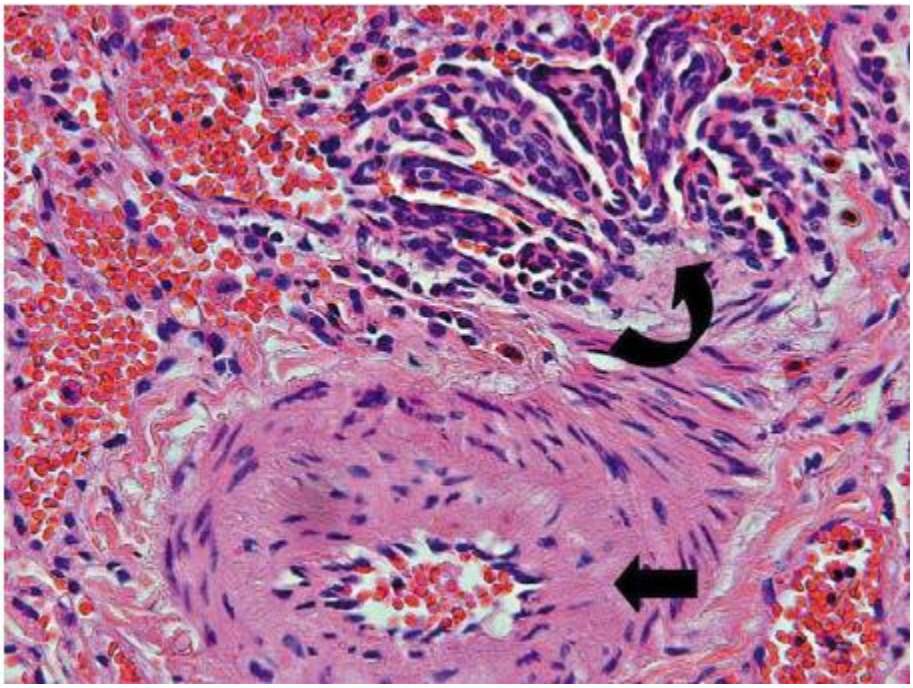
- Embolic material → via portosystemic shunts → enter lungs

Plexogenic factors:[66,67]

- Bypassed vasoactive substances
- Produce plexogenic arteriopathy
- Increased pulmonary blood flow & proliferation of smooth muscle → endothelial damage and vascular remodeling

Risk of developing pulmonary hypertension – increases with duration of portal hypertension

Figure 19: Histology of lung in portopulmonary hypertension



Intimal and medial thickening of pulmonary artery (straight arrow)

Channel like structures forming plexiform lesions (curved arrow)

CLINICAL FEATURES

- Asymptomatic in most patients
- Exertional dyspnea → dyspnea at rest
- Fatigue

- Syncope
- Chest pain
- Elevated JVP
- Loud pulmonary component (P2) of 2^{nd} heart sound
- Systolic murmur
- Severe pulmonary hypertension[68]

DIAGNOSIS

- Electrocardiogram
  - Right atrial enlargement
  - Right ventricular hypertrophy
  - Right bundle branch pattern.
- Chest X-Ray
  - Pulmonary arteries – prominent
  - Cardiomegaly
- Computed Tomography:[69]
  - Evidence of pulmonary hypertension – main pulmonary artery diameter ≥29 mm
- Echocardiogram

- Noninvasive screening test
- Elevated right ventricular systolic pressure (RVSP)
- Tricuspid regurgitant jet → Pulmonary hypertension[91]

➢ Right heart catheterization[94]

- Confirmation of PPH
- Measures pulmonary artery pressure

PROGNOSIS:

Mean survival – 15 months

High perioperative mortality[68]

Screening for portopulmonay hypertension – mandatory in patients awaiting liver transplantation

TREATMENT OF PORTOPULMONARY HYPERTENSION:

- Vasodilators - mainstay of therapy, reverses the vasoconstriction
- Prostacyclin[95] – epoprostenol[70,71,72], iloprost → vasodilator & platelet aggregation inhibitor
- Endothelin receptor antagonists – Bosentan[73,74], Ambrisentan

- Inhaled Nitric Oxide
- Phosphodiesterase inhibitors[75]
- L-arginine
- Diuretics

Liver transplantation:

Role of OLT (orthotopic liver transplantation) – controversial

Not the curative treatment in PPH

Contraindicated in patients with mean PAP > 50 mm Hg

Liver Transplantation – indicated in selected patients[76] after clinical improvement by medical therapy

Medical therapy – used to bridge PPH patients to OLT[77]

MATERIALS & METHODS

MATERIALS AND METHODS

SOURCE OF DATA:

Patients admitted in Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 diagnosed to have Cirrhosis of liver, fulfilling the inclusion and exclusion criteria were included in the study group. 40 such patients were taken up for this study.

STUDY DESIGN:

A hospital based observational study

STUDY DURATION:

6 months: March 2014-August 2014

INCLUSION CRITERIA:

- Proven cases of cirrhosis of liver by clinical, endoscopic and sonographic evidence.

EXCLUSION CRITERIA:

- Patients with coexisting primary pulmonary diseases like COPD, Bronchial asthma, ILD etc.
- Coexisting intrinsic heart disease.
- Patients with life threatening complications of cirrhosis like active upper gastrointestinal haemorrhage, hepatic encephalopathy.
- Smokers.

DATA COLLECTION AND METHODS:

Data was collected in a pretested proforma from eligible patients. 40 patients were selected on the basis of simple random sampling. They were subjected to detailed history taking and clinical examination. The following investigations were done.

- Complete blood count
- LFT
- RFT with electrolytes
- Chest X-ray
- Electrocardiogram
- Viral markers

- USG of abdomen,
- Upper gastrointestinal endoscopy,
- Arterial blood gas analysis
- Pulmonary function test
- Contrast Echocardiogram

ABG:

Arterial blood gas analysis was done by a single radial puncture under local anaesthesia, while the patient was in the supine position breathing room air and the sampling was repeated with the patients standing ,breathing 100% oxygen. Each of these positions was maintained for a minimum of 10 min.

The presence of hypoxemia and orthodeoxia was also detected. Orthodeoxia is defined as fall in PaO_2 levels more than 3mmHg on changing position from supine to standing and hypoxemia if PaO_2 is less than 70mmHg in any position at rest. Alveolar Arterial gradient of partial pressure of oxygen was taken as elevated if it were elevated more than 30mmHg (calculated as P (A-a) O_2=PaO_2-150-1.25x$PaCO_2$).

PFT – Pulmonary function test:

All patients were subjected to PFT using spirometer in the standing position according to standard procedures.

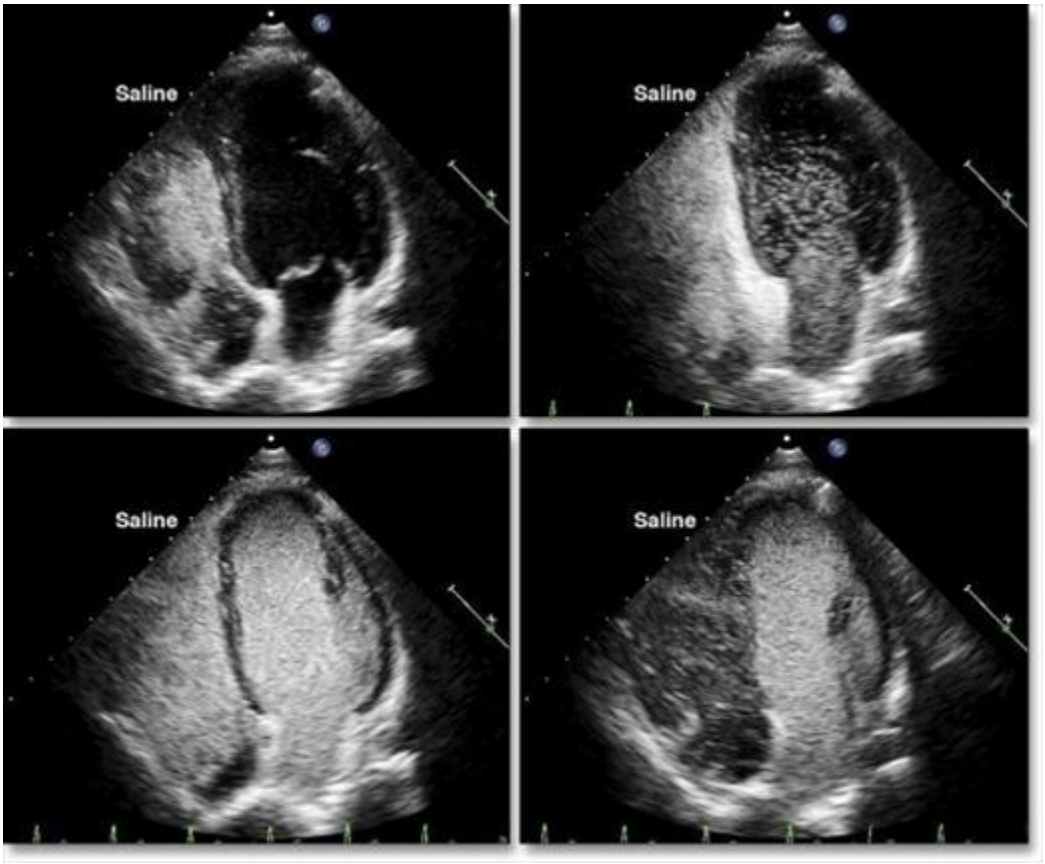
- Forced expiratory volume in one second (FEV1),
- Forced vital capacity (FVC),
- Peek Expiratory Flow Rate (PEFR)

Predicted values for each of the parameters were obtained from standardized references.

Echocardiogram:

A 2-D transthoracic contrast enhanced echocardiography was done for all patients. Contrast-enhanced echocardiography with agitated saline was done to detect pulmonary vascular dilatation. 10ml of agitated solution of normal saline was administered to all the patients in the supine position. A positive test was defined as any visualization of microbubbles in the left heart chambers after three cardiac cycles after its appearance in the right ventricle in any of three injections

Figure 20: Contrast echocardiogram showing intrapulmonary shunting



Hepatopulmonary syndrome in cirrhosis identified by

- Delayed positive contrast echocardiography
    - microbubble visualization in left atrium occurring within 3 to 6 beats after its visualization on right side
- Abnormal oxygenation
    - PaO_2 <70mmHg or
    - $P(A\text{-}a)O_2$ >20mmHg in any position (supine, standing)

STASTICAL METHODS APPLIED:

Datas were analysed using the SPSS software. Statistical significance was indicated by the Chisquare test. Variables were considered to be significant if $p<0.05$

OBSERVATION

&

RESULTS

OBSERVATION AND RESULTS

Table 1. AGE DISTRIBUTION

Age group (years)	Frequency	Percent
20 -30	6	15.0
31-40	13	32.5
41-50	10	25.0
51- 60	9	22.5
>60	2	5.0
Total	40	100.0

Most cases of cirrhosis (13 patients) occur in the age group of 31-40 (32.5%) years

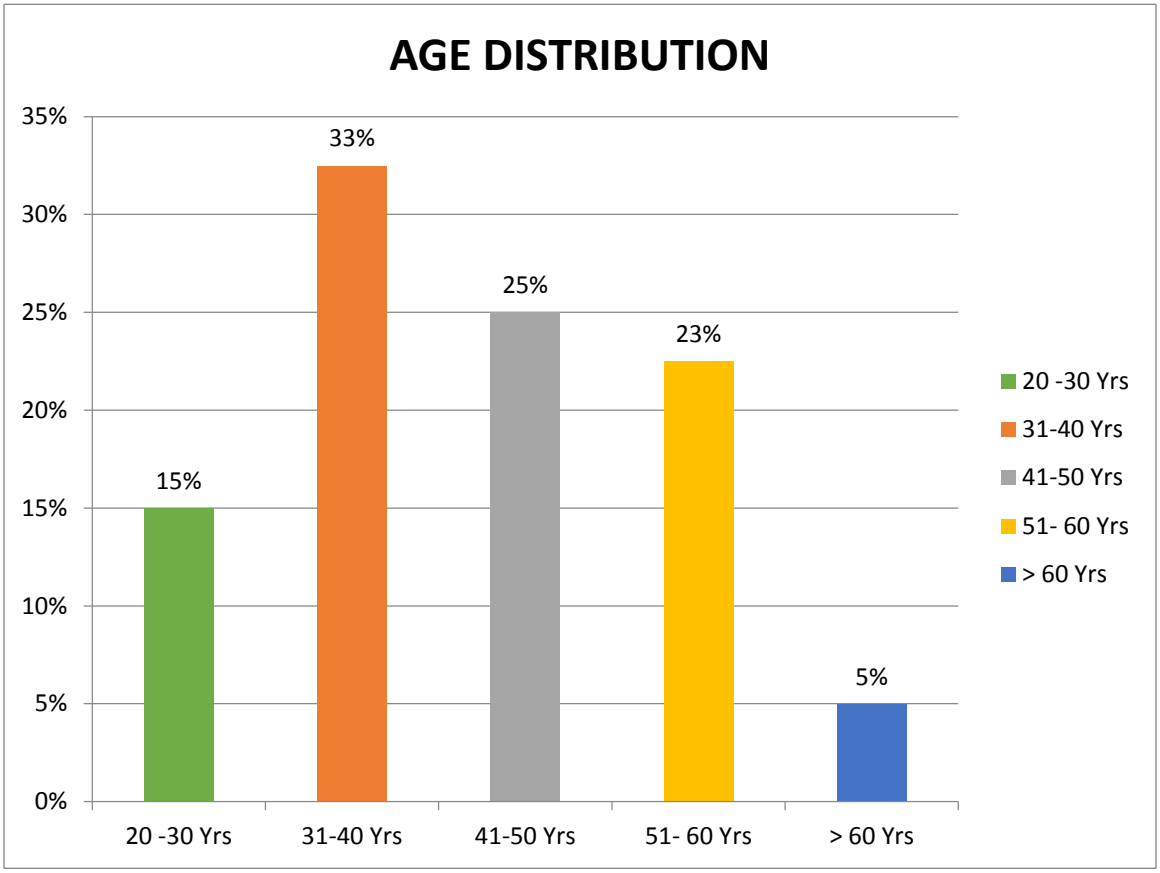
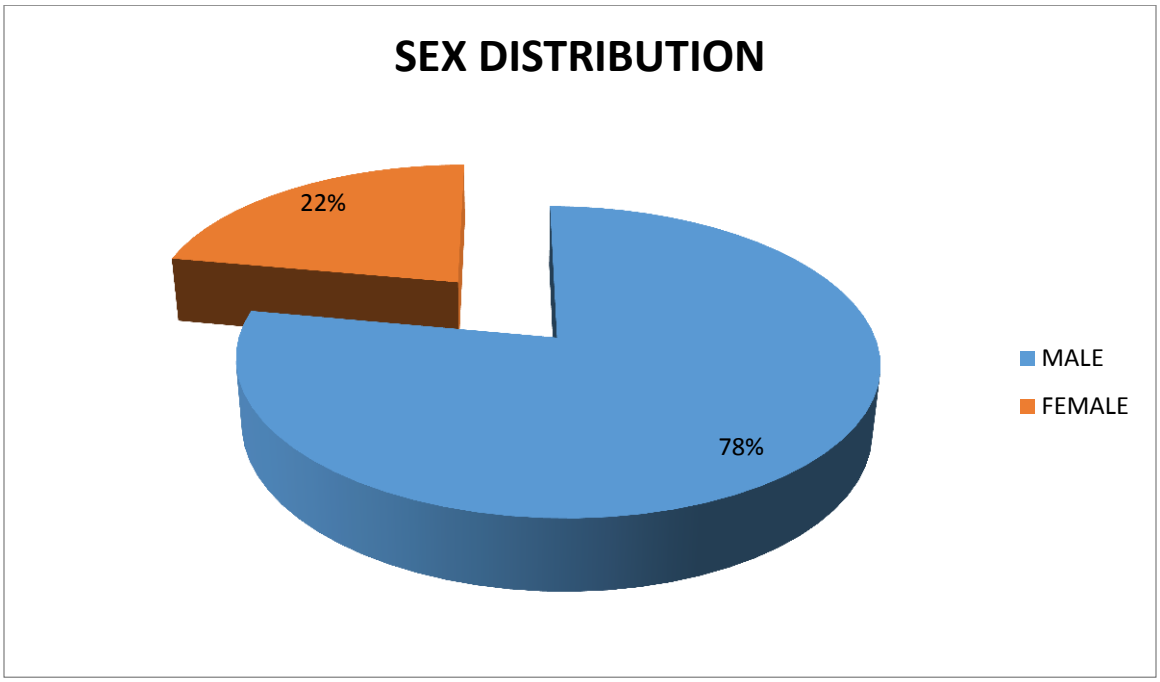

AGE DISTRIBUTION
35%
30%
25%
20%
15%
10%
5%
0%
33%
25%
23%
15%
5%
20 -30 Yrs
31-40 Yrs
41-50 Yrs
51- 60 Yrs
> 60 Yrs
20 -30 Yrs
31-40 Yrs
41-50 Yrs
51- 60 Yrs
> 60 Yrs

Table 2. SEX DISTRIBUTION

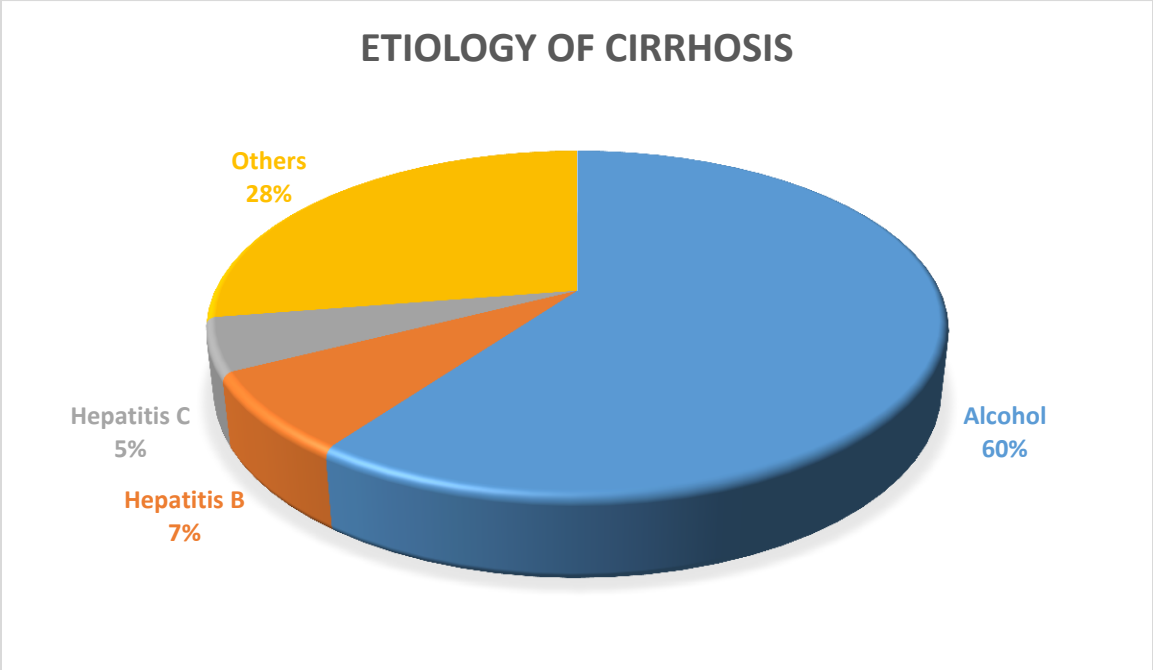
	Frequency	Percent
MALE	31	77.5
FEMALE	9	22.5
Total	40	100.0



Among 40 patients included in our study, 31patients (78%) were males and 9 patients (22%) were females

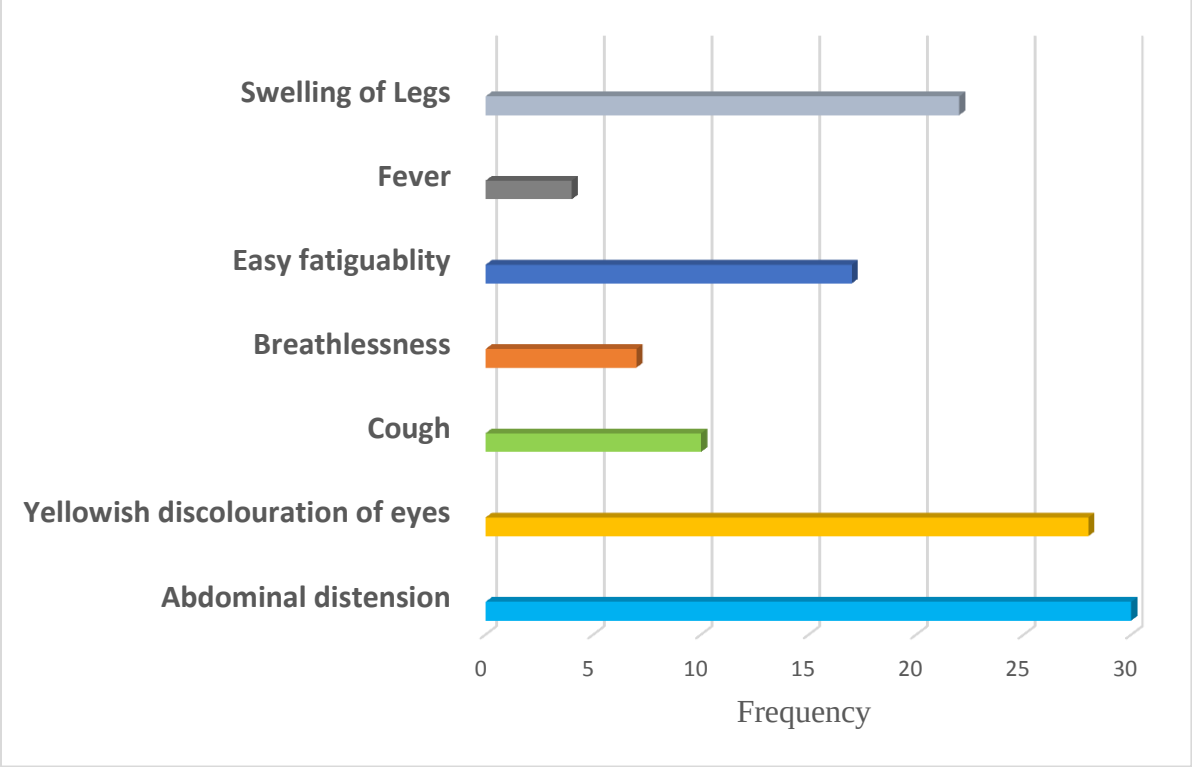
Table 3. ETIOLOGY OF CIRRHOSIS

Etiology	Frequency	Percent
Alcohol	24	60.0
Hepatitis B virus	3	7.5
Hepatitis C virus	2	5.0
Others	11	27.5
Total	40	100



In our study, the most common cause for cirrhosis in the study group was alcohol seen in 24 patients (60%).

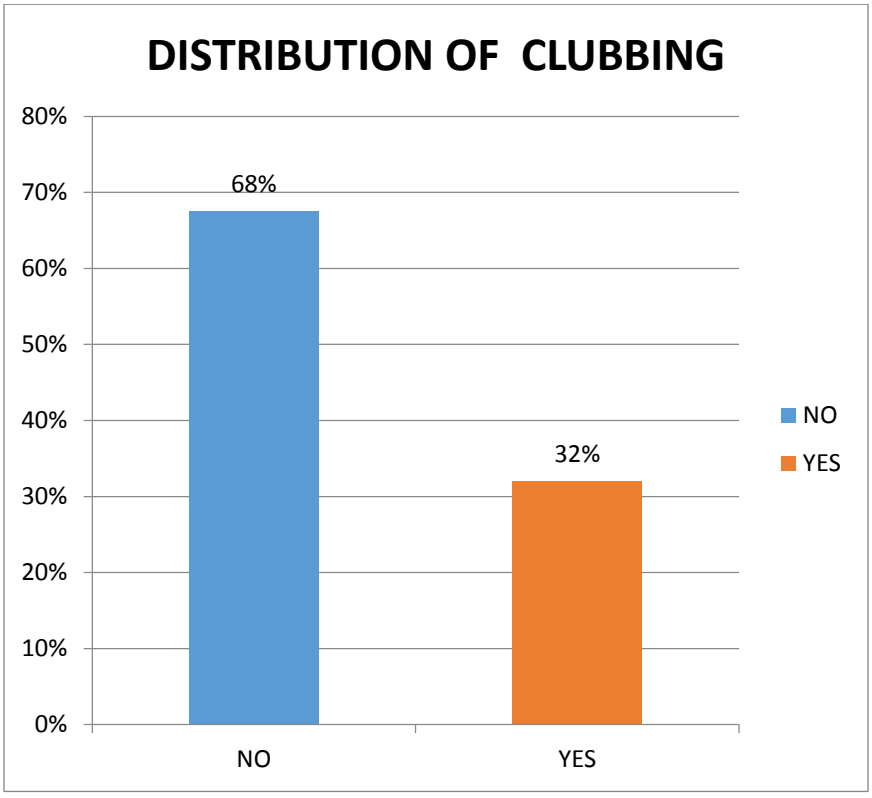
DISTRIBUTION OF PRESENTING COMPLAINTS AMONG CASES



In our study, abdominal distension was the most common presenting symptom present in 30 patients (75%). The most common respiratory symptom was cough present in 10 patients (25%) followed by breathlessness in 7 patients (17.5%)

Table 4. DISTRIBUTION OF CLUBBING

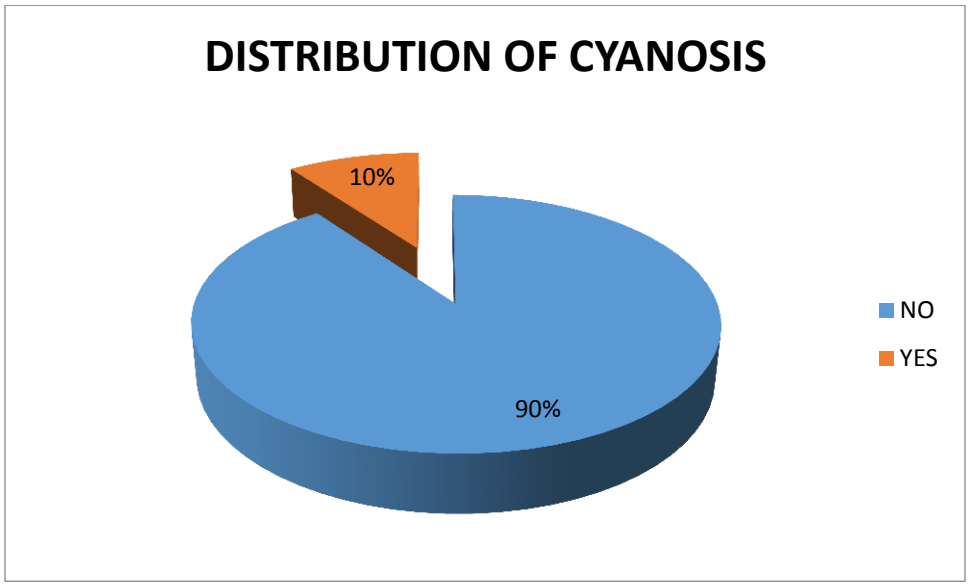
	Frequency	Percent
NO	27	67.5
YES	13	32.5
Total	40	100.0



Among 40 cirrhotic patients, clubbing was seen in 13 patients (32%)

Table 5. DISTRIBUTION OF CYANOSIS

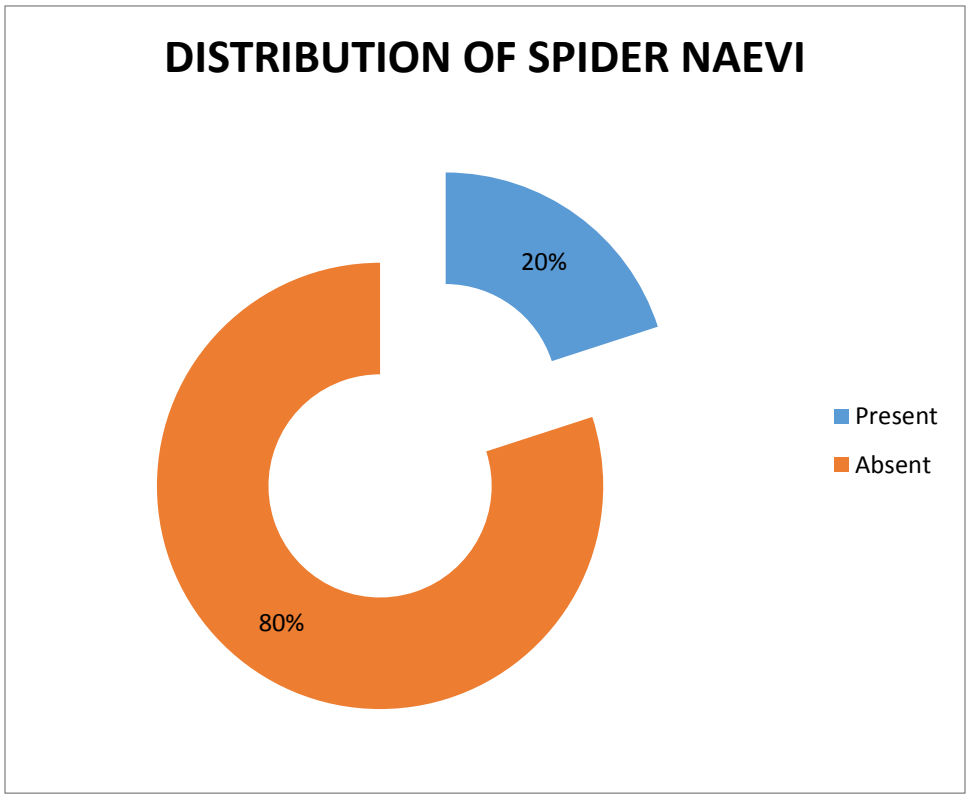
	Frequency	Percent
NO	36	90.0
YES	4	10.0
Total	40	100.0



Out of the 40 cirrhotic patients, cyanosis was seen in 4 patients (10%)

Table 6. DISTRIBUTION OF SPIDER NAEVI

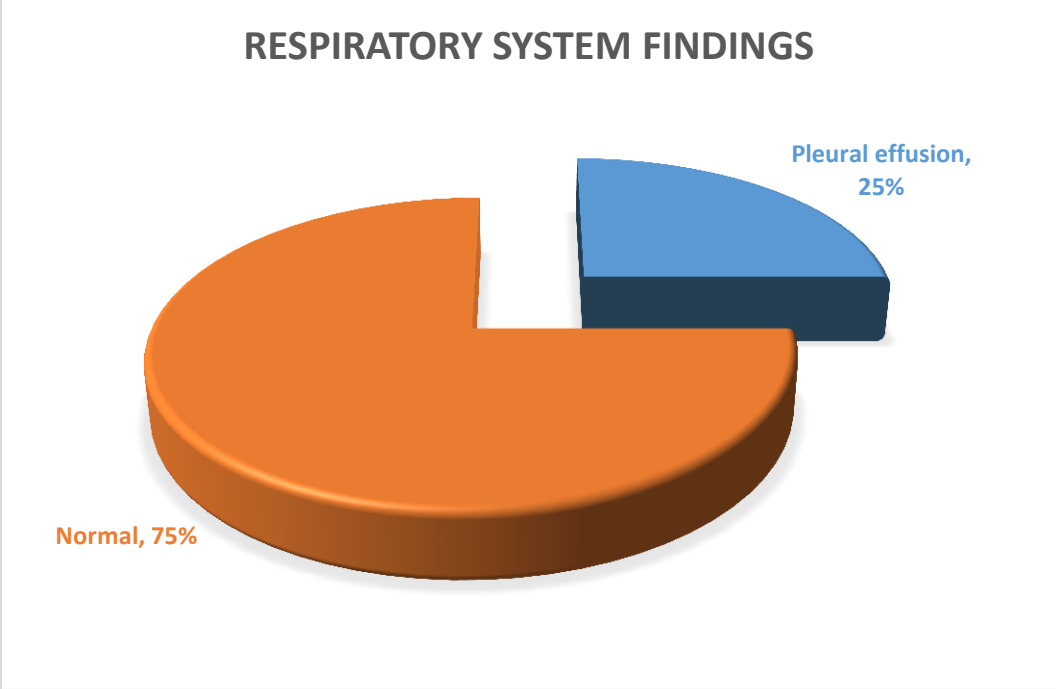
	Frequency	Percent
PRESENT	8	20.0
ABSENT	32	80.0
Total	40	100.0



In our study of 40 patients, spider naevi was seen in 8 patients (20%)

Table 7. RESPIRATORY SYSTEM FINDINGS

	Frequency	Percent
Pleural effusion	10	25
Normal	30	75
Total	40	100.0



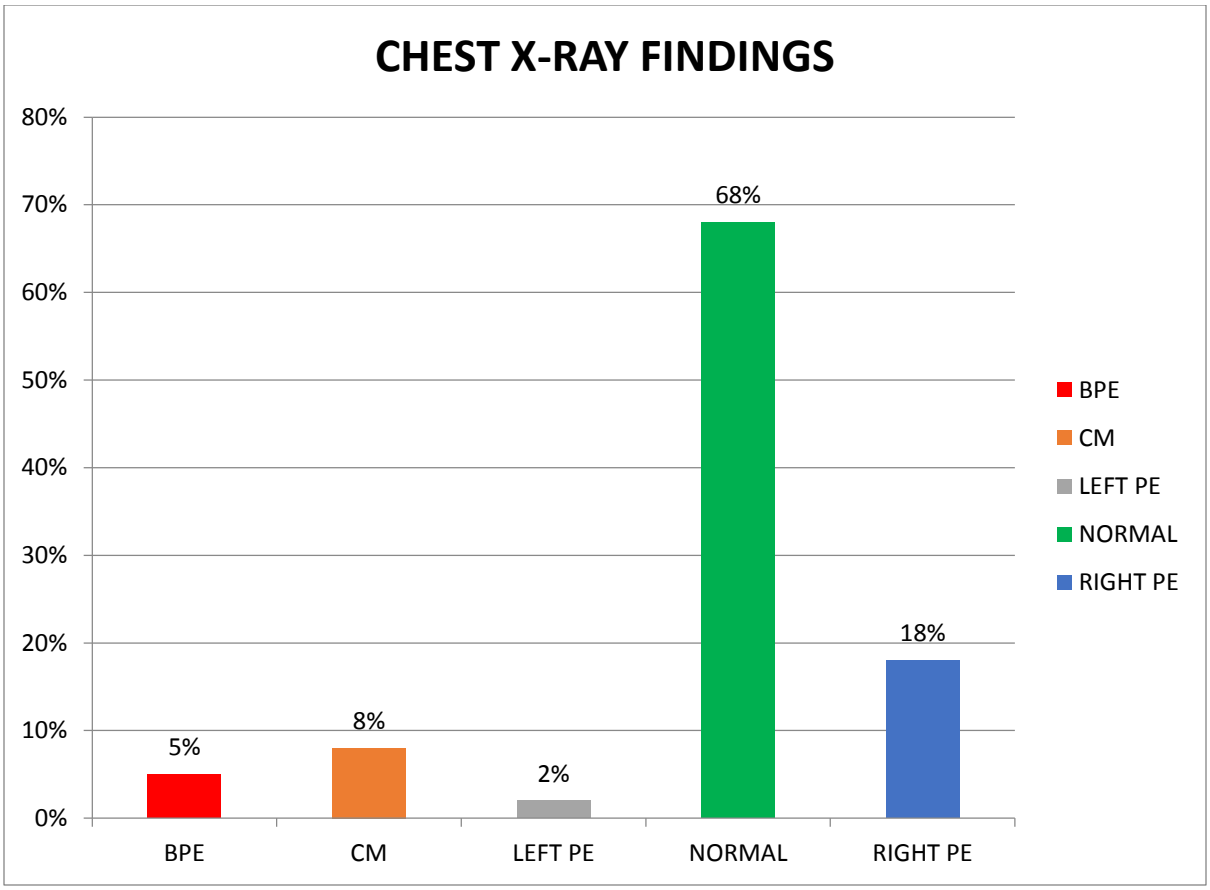
In our study, respiratory system examination showed pleural effusion in 10 patients (25%) which is the most common pulmonary finding in patients with cirrhosis of liver.

Table 8. CHEST X-RAY FINDINGS

	Frequency	Percent
BPE	2	5.0
CM	3	7.5
LPE	1	2.5
N	27	67.5
RPE	7	17.5
Total	40	100.0

BPE – bilateral pleural effusion, CM – cardiomegaly, LPE – left pleural effusion, RPE – right pleural effusion, N – normal x-ray

In our study right sided pleural effusion was seen in 7 patients (17.5%), left sided pleural effusion was seen in 1 patient (2.5%), bilateral pleural effusion was seen in 2 patients (5%), cardiomegaly was seen in 3 patients (7.5%) and normal chest x-ray was seen 27 patients (67.5%)

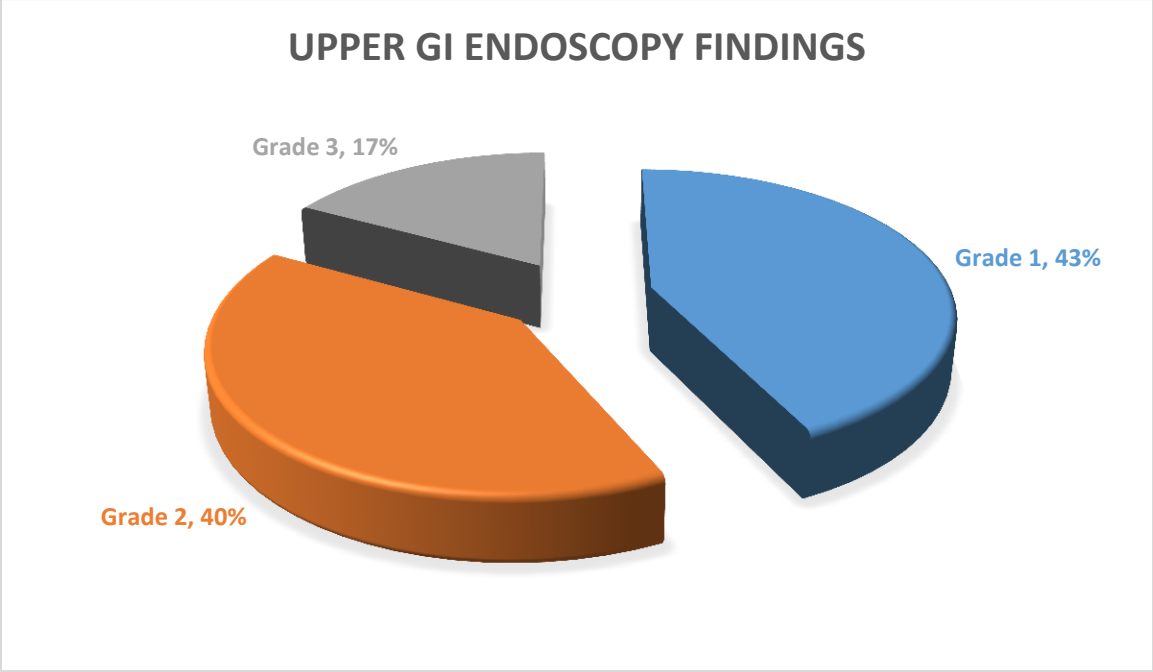


BPE – bilateral pleural effusion, CM – cardiomegaly, LEFT PE – left pleural effusion, RIGHT PE – right pleural effusion

In chest x-ray, right pleural effusion was more common, followed by cardiomegaly and bilateral pleural effusion. Left pleural effusion was less commonly seen

Table 9. UPPER GI ENDOSCOPY FINDINGS

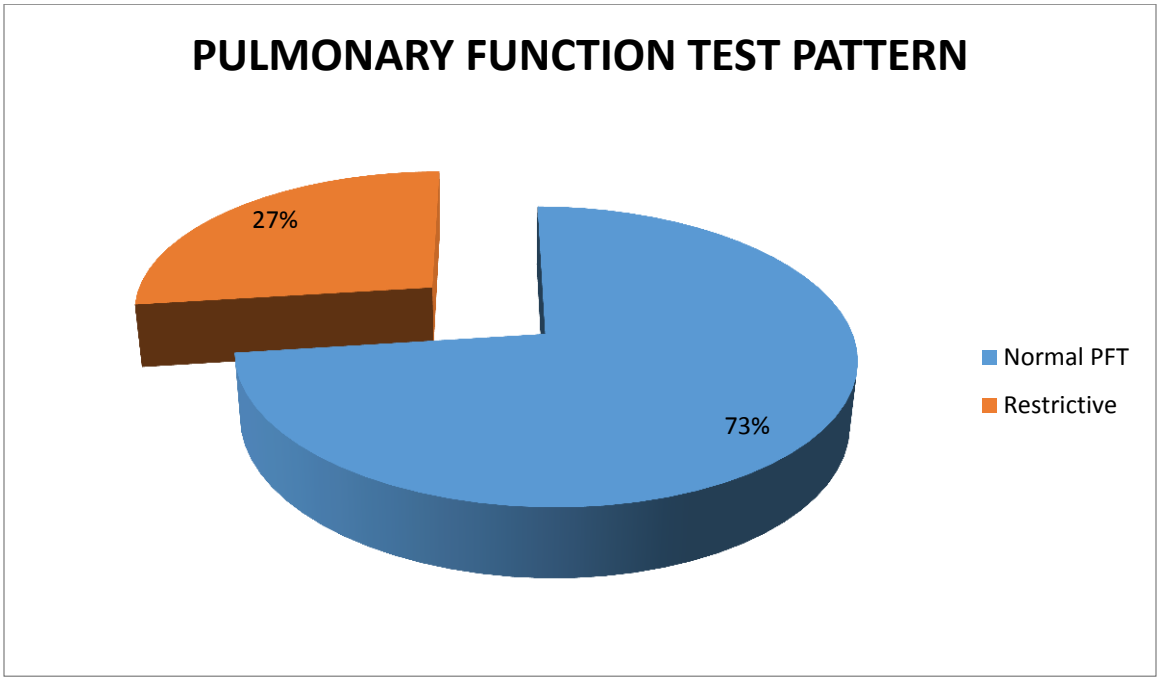
Esophageal varices (EV)	Frequency	Percent
Grade 1	17	42.5
Grade 2	16	40.0
Grade 3	7	17.5
Total	40	100.0



In our study, 17 patients (42.5%) showed Grade 1 varices, 16 patients (40%) showed Grade 2 varices and 7 patients (17.5%) showed Grade 3 varices.

Table 10. DISTRIBUTION OF PFT PATTERN

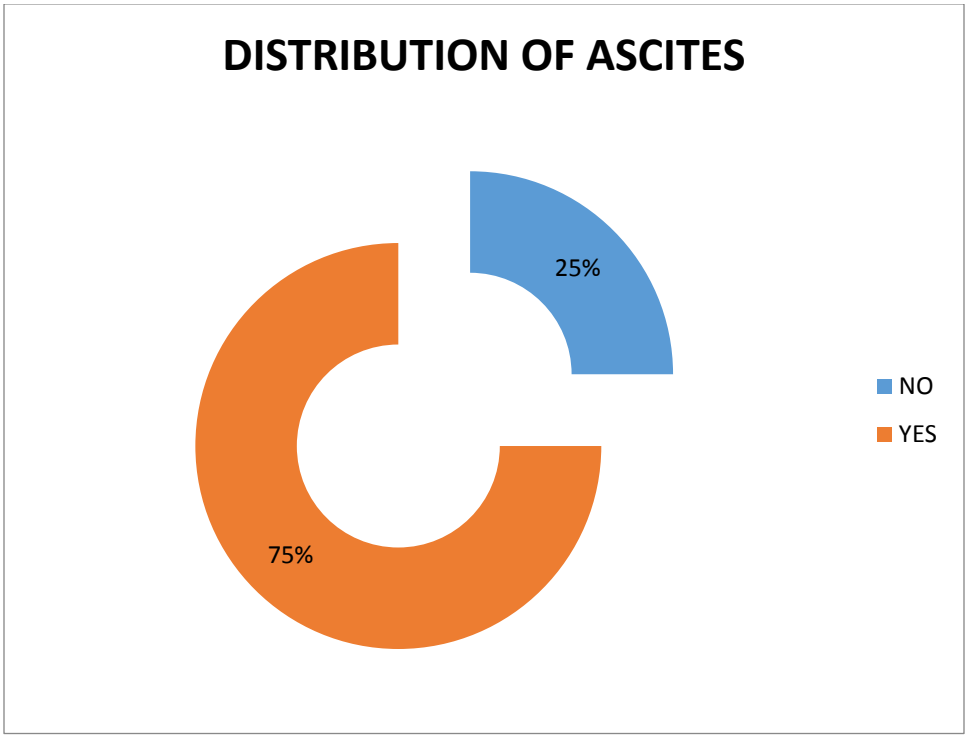
	Frequency	Percent
Normal	29	72.5
Restrictive	11	27.5
Total	40	100.0



In our study, 29 patients (72.5%) showed normal pulmonary function tests by spirometry whereas 11 patients (27.5%) showed restrictive pattern of lung disease.

Table 11. DISTRIBUTION OF ASCITES

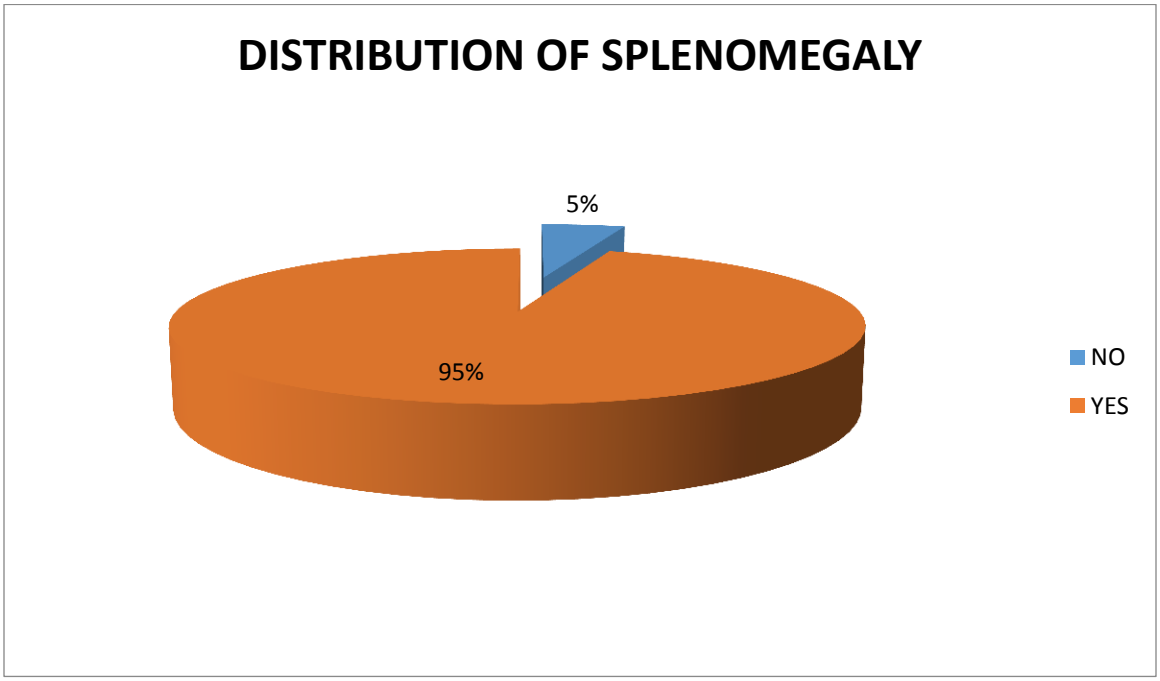
	Frequency	Percent
NO	10	25.0
YES	30	75.0
Total	40	100.0



In our study, ascites was seen in 30 patients (75%) whereas ascites was absent in 11 patients (25%)

Table 12. DISTRIBUTION OF SPLENOMEGALY

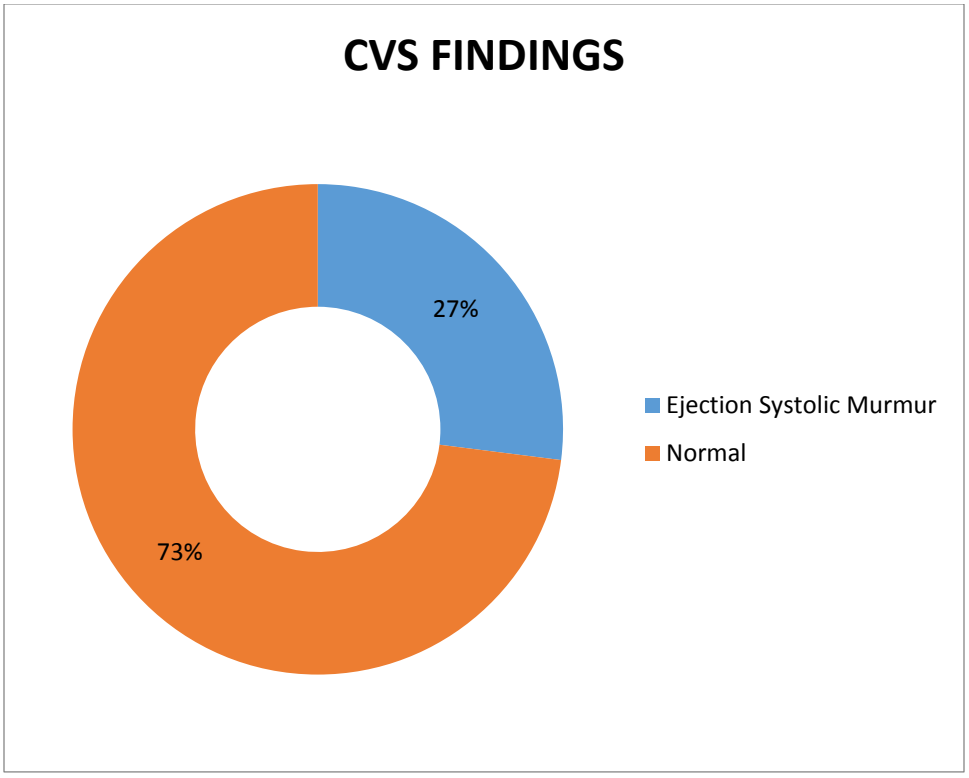
	Frequency	Percent
NO	2	5.0
YES	38	95.0
Total	40	100.0



In our study of 40 patients, splenomegaly was predominantly present in 38 patients (95%)

Table 13. CVS FINDINGS

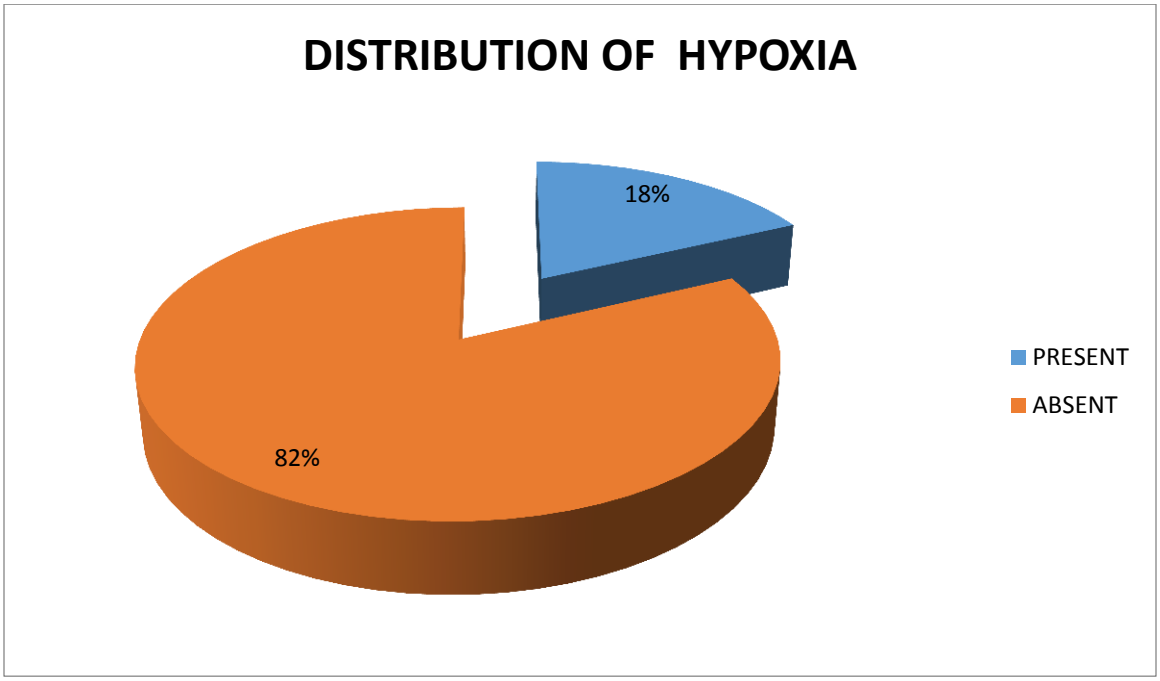
	Frequency	Percent
ESM	11	27.5
Normal	29	72.5
Total	40	100.0



In our study, cardiovascular system examination was normal in 29 patients (72.5%) whereas Ejection systolic murmur (ESM) was present in 11 patients (27.5%)

Table 14. DISTRIBUTION OF HYPOXIA AMONG CASES

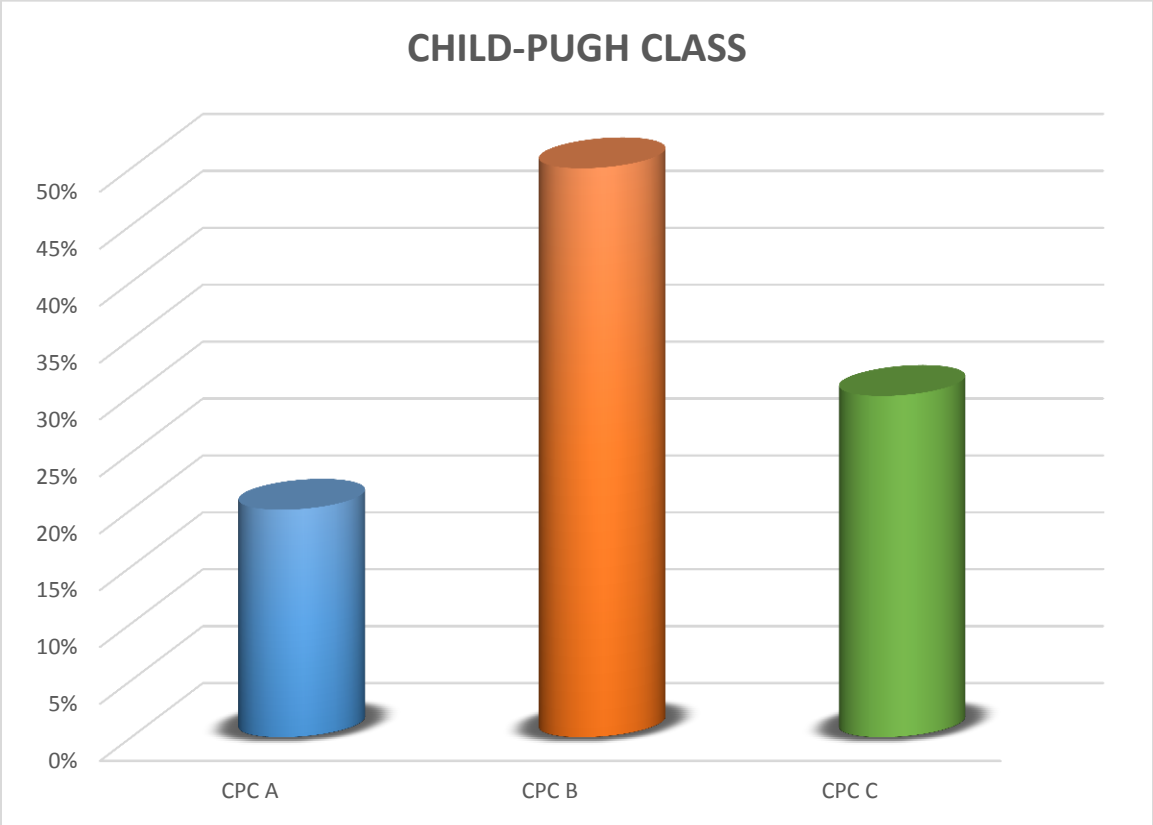
	Frequency	Percent
PRESENT (PaO2 <70)	7	17.5
ABSENT	33	82.5
Total	40	100.0



In our study of 40 cirhhotic patients, hypoxia (PaO2 <70 mm Hg) was present in 7 patients (17.5%)

Table 15. CHILD PUGH CLASS

CPC class	Frequency	Percent
A	8	20.0
B	20	50.0
C	12	30.0
Total	40	100.0

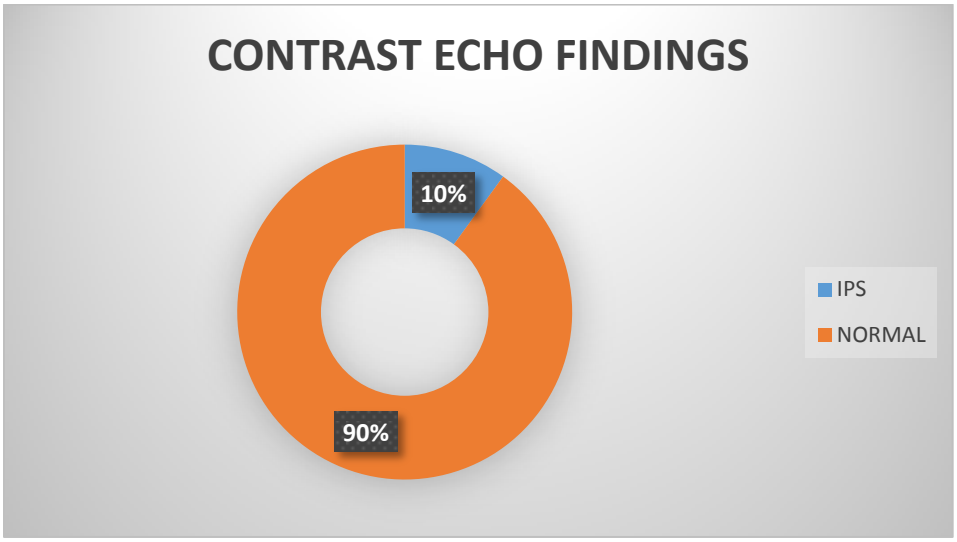


In our study of 40 cirrhotic patients, 8 patients (20%) were in Child-Pugh class A, 20 patients (50%) were in Child-Pugh class B and 12 patients (30%) were in Child-Pugh class C

Table 16. CONTRAST ECHOCARDIOGRAM FINDINGS

	Frequency	Percent
IPS	4	10.0
N	36	90.0
Total	40	100.0

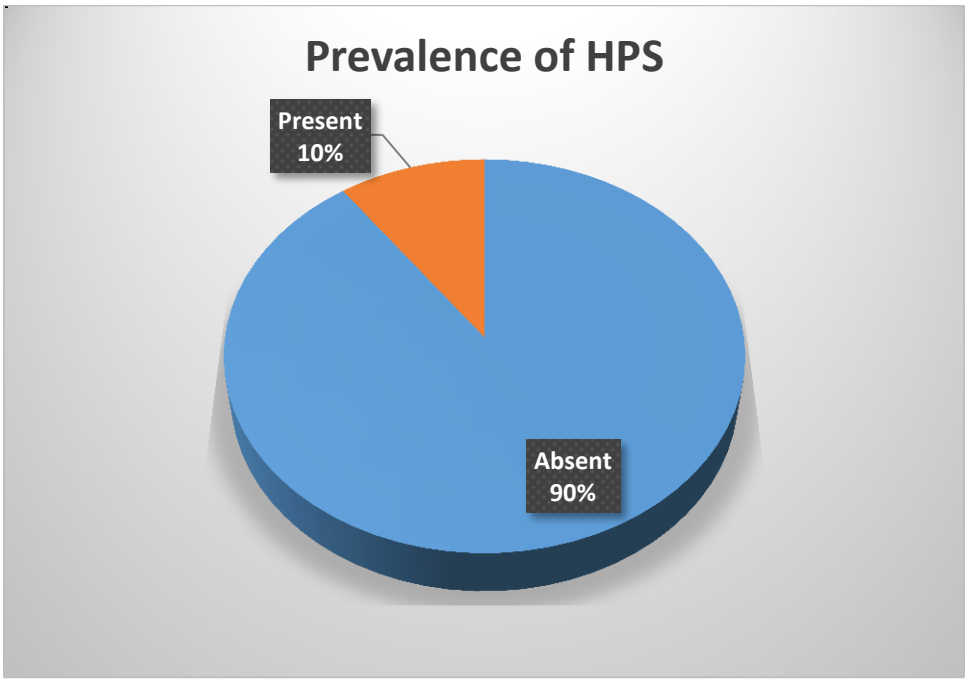
IPS – intrapulmonary shunting, N – normal study



In our study, 4 patients (10%) showed intrapulmonary shunting in contrast echocardiogram

Table17. PREVALENCE OF HEPATOPULMONARY SYNDROME AMONG CIRRHOTICS

Hepatopulmonary syndrome (Hypoxia + IPS)	Frequency	Percent
Present	4	10
Absent	36	90
Total	40	100

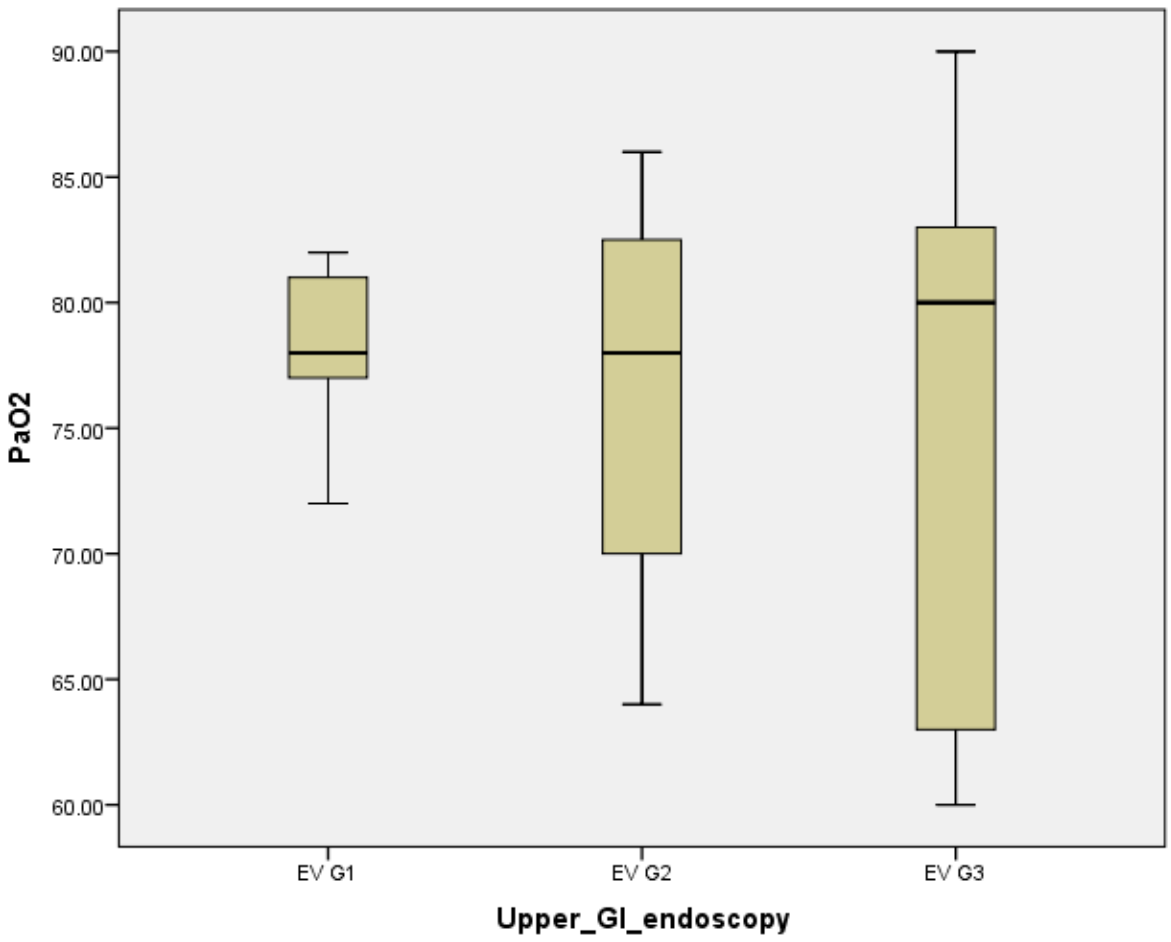


In our study of 40 cirrhotic patients, hepatopulmonary syndrome was present in 4 patients (10%)

Table 18. CORRELATION BETWEEN GRADING OF VARICES AND PaO_2 & FEV1

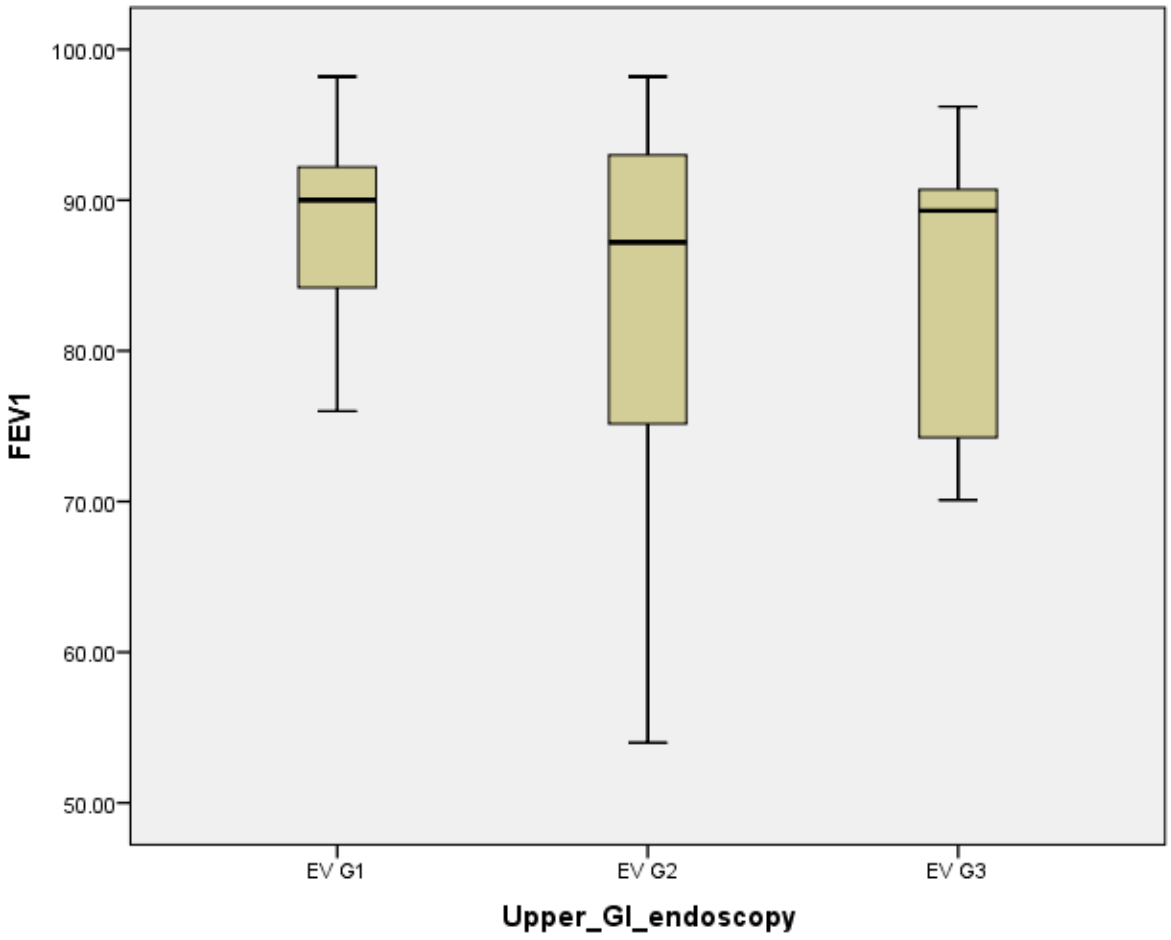
	Grading of varices	Mean	SD	Minimum	Maximum	Range	CORRELATION	P VALUE
PaO2	1	77.94	3.83	72.00	82.00	10.00	-0.43	**0.01**
	2	76.69	7.17	64.00	86.00	22.00		
	3	74.57	12.30	60.00	90.00	30.00		
FEV1	1	88.21	6.69	76.00	98.20	22.20	-0.19	0.23
	2	82.68	13.25	54.00	98.20	44.20		
	3	83.64	10.45	70.10	96.20	26.10		

Figure 21. CORRELATION BETWEEN GRADING OF VARICES & PaO_2



In our study, PaO2 was compared with the grading of varices. It was found that there was a decrease in PaO2 with severity of varices which was statistically significant with p-value 0.01

Figure 22: CORRELATION BETWEEN GRADING OF VARICES & FEV1

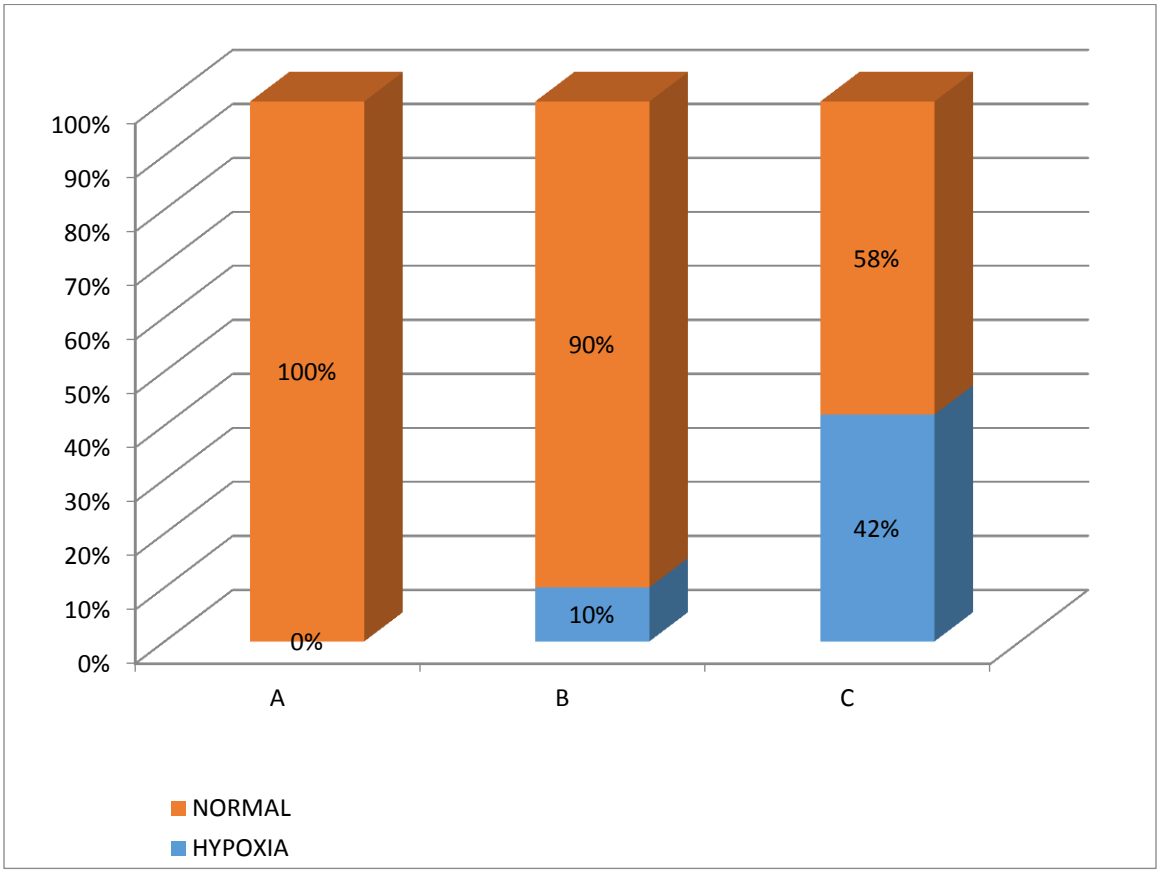


In our study, FEV1 was compared with the grading of varices. It was found that there was no significant correlation between FEV1 and grading of varices.

Table 19. CORRELATION BETWEEN PaO_2 & SEVERITY OF LIVER DISEASE (CHILD PUGH CLASS)

			Child Pugh class (CPC)					
			A	B	C	Total	CORRELATION	P VALUE
PaO2	HYPOXIA	Count	0	2	5	7		
	NORMAL	Count	8	18	7	33		
Total		Count	8	20	12	40	-0.41	**0.01**

CORRELATION BETWEEN PaO_2 & SEVERITY OF LIVER DISEASE (CHILD PUGH CLASS)

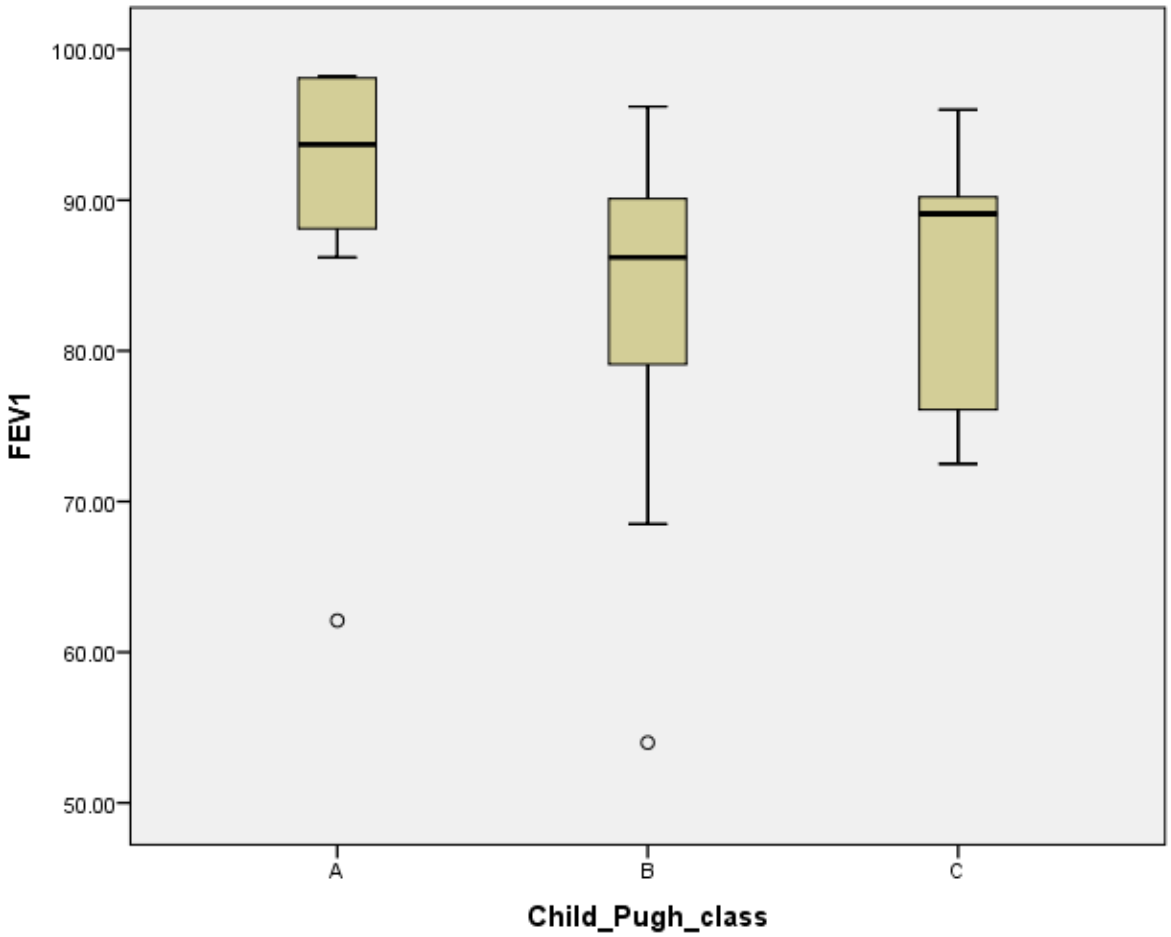


In our study, PaO2 was correlated with the severity of liver disease (by Child-Pugh class). It was found that there was a decrease in PaO2 with severity of liver disease which was statistically significant with p-value 0.01

Table 20. CORRELATION BETWEEN FEV1 & SEVERITY OF LIVER DISEASE (CHILD-PUGH CLASS)

	Child Pugh class	Mean	SD	Minimum	Maximum	Range	CORRELATION	P VALUE
FEV1	A	90.0125	12.13736	62.10	98.20	36.10	-0.17	0.30
	B	83.7900	10.80691	54.00	96.20	42.20		
	C	84.3333	8.50030	72.50	96.00	23.50		

Figure 23: CORRELATION BETWEEN FEV1 & SEVERITY OF LIVER DISEASE (CHILD-PUGH CLASS)



In our study, FEV1 was correlated with the severity of liver disease (by Child-Pugh class). It was found that there was no significant correlation between FEV1 and severity of liver disease

Table 21. CORRELATION BETWEEN PFT & SEVERITY OF LIVER DISEASE (CHILD-PUGH CLASS)

Child Pugh class		PFT Pattern		Total		
		N	R		Chi square	P value
A	Count	7	1	8	4.514	0.105
B	Count	16	4	20		
C	Count	6	6	12		
Total		29	11	40		

In our study, PFT was correlated with the severity of liver disease among the study group. No significant correlation was obtained from our study and it is not statistically significant.

CORRELATION BETWEEN PFT & SEVERITY OF LIVER DISEASE (CHILD-PUGH CLASS)

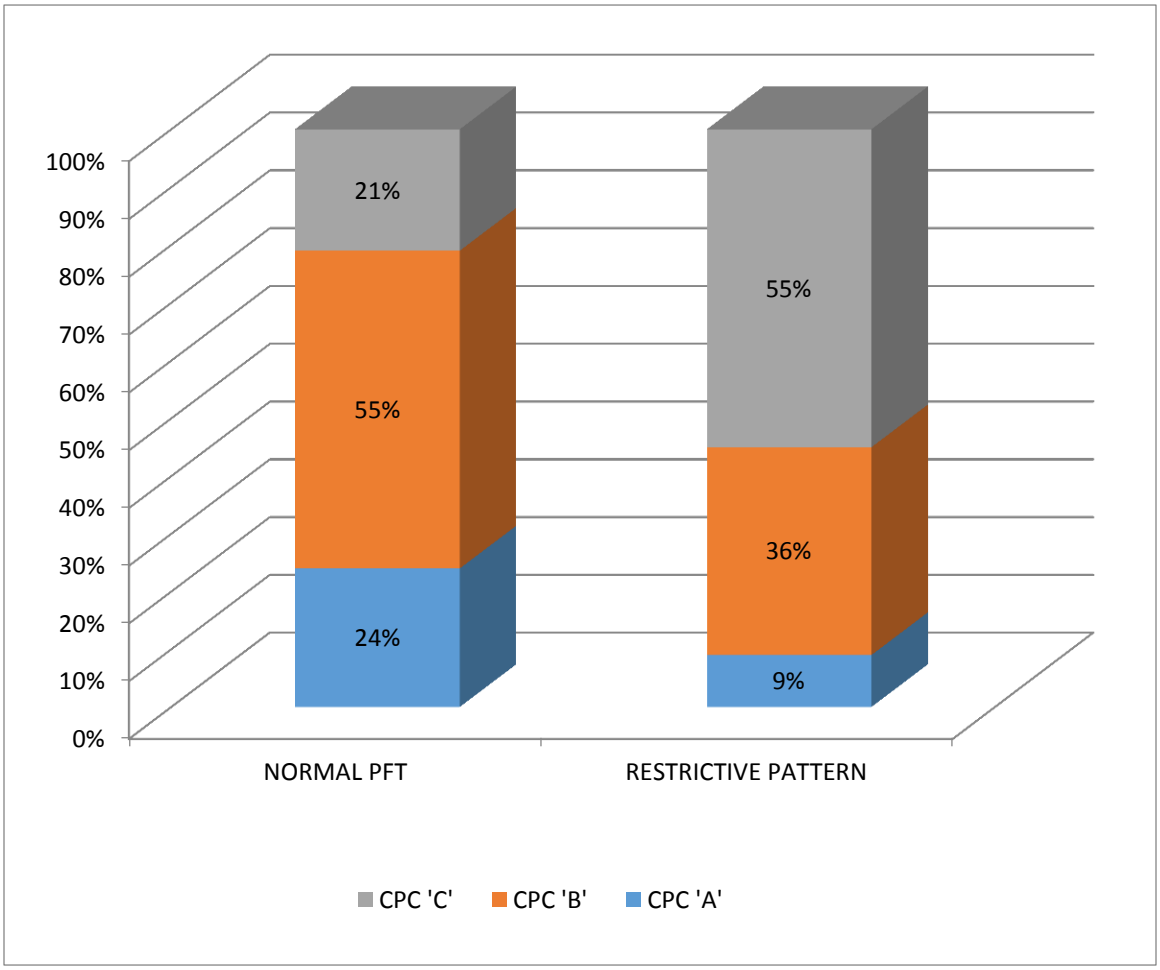
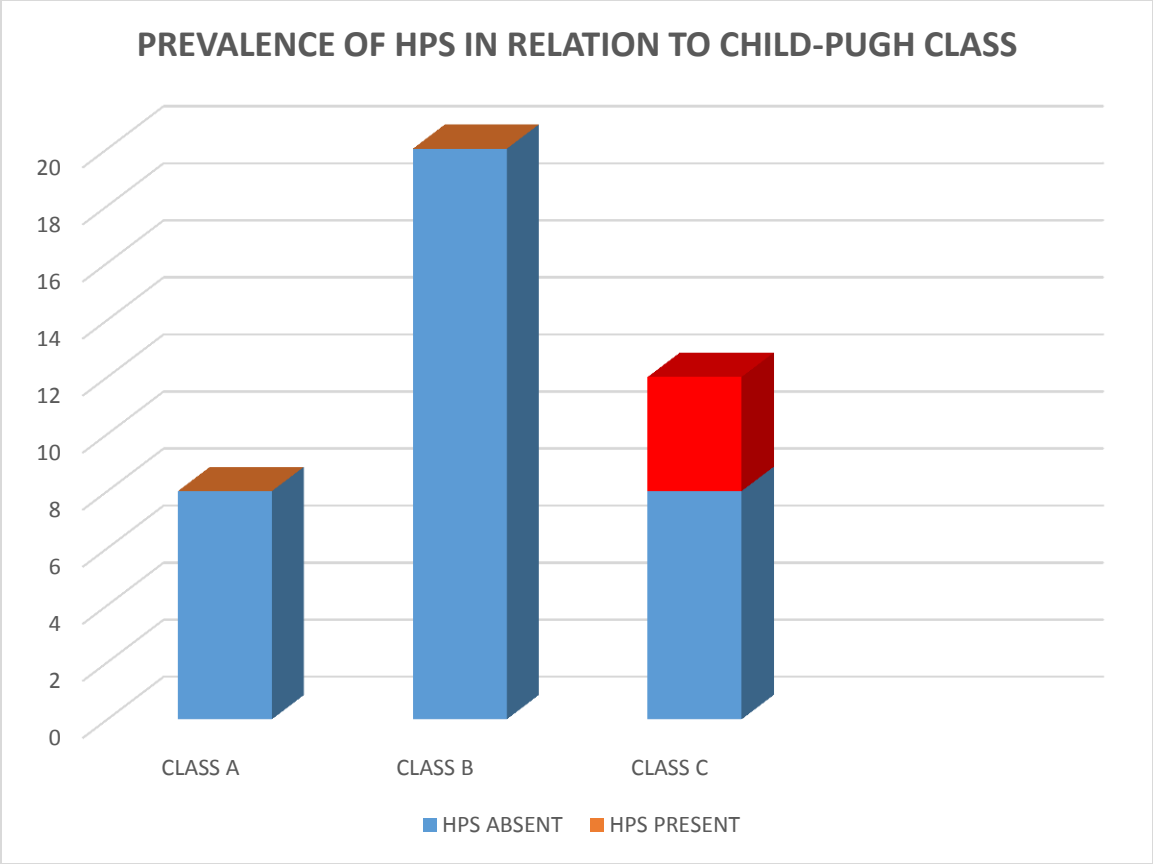
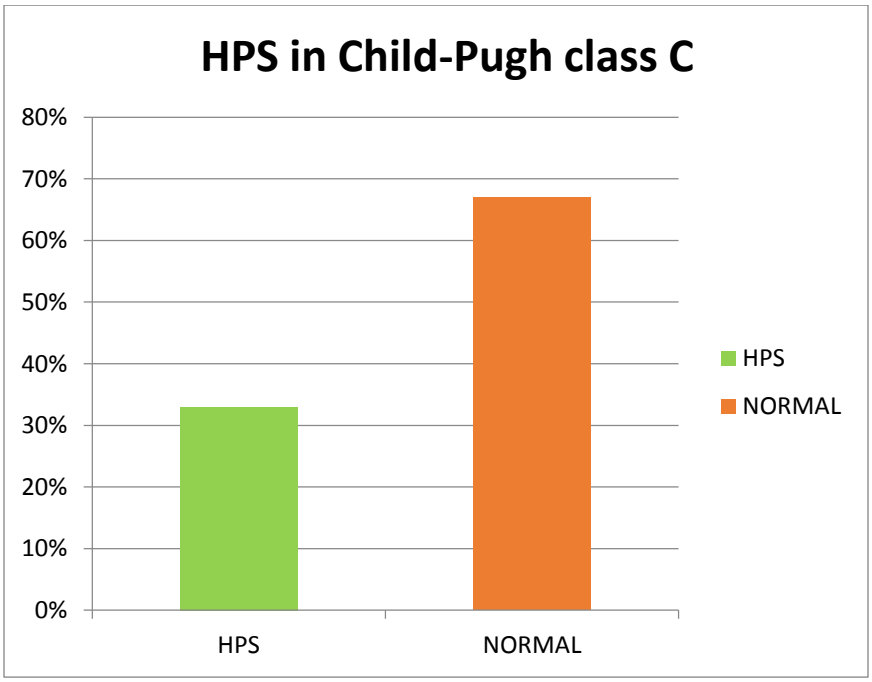


Table 22. CORRELATION BETWEEN CHILD-PUGH CLASS & HPS

			HPS		Total		
			YES	NO		Chi square	p value
Child Pugh class	A	Count	0	8	8	10.370	**0.006**
	B	Count	0	20	20		
	C	Count	4	8	12		
Total			4	36	40		

In our study, prevalence of HPS was correlated with the severity of liver disease (by Child-Pugh class). All the 4 patients with HPS were under Child-Pugh class C. This indicates that the prevalence of HPS increases with increasing severity of liver disease. This was statistically significant in our study with p-value 0.006


PREVALENCE OF HPS IN RELATION TO CHILD-PUGH CLASS
20
18
16
14
12
10
8
6
4
2
0
CLASS A
CLASS B
CLASS C
HPS ABSENT
HPS PRESENT


HPS in Child-Pugh class C
80%
70%
60%
50%
40%
30%
20%
10%
0%
HPS
NORMAL
HPS
NORMAL

DISCUSSION

DISCUSSION

Our study was conducted in patients with cirrhosis of liver to know the prevalence of hepato-pulmonary syndrome. Our study population included 40 patients who were diagnosed as cirrhosis of liver either by clinical, endoscopic or sonographic evidence. All 40 patients were evaluated for presence of hypoxemia and were screened for the presence of hepato-pulmonary syndrome. Analysis was made to study the correlation between hypoxemia & severity of liver disease, hypoxemia & grading of varices, and to establish the correlation between severity of liver disease and prevalence of hepato-pulmonary syndrome using Chi-square test. Following were the observations made from our study in cirrhotic patients.

Age distribution:

Out of 40 patients, majority of cases were in the age group of 31-40 years (32.5%). This showed that cirrhosis is most commonly seen in young adults.

Sex distribution

Out of 40 patients in this study, 31 patients (77.5%) were males and 9 patients (22.5%) were females. Male to female ratio is 3:1.

Etiology

Among 40 patients, Alcohol was the most common etiology in 24 patients (60%) followed by other causes of cirrhosis in 11 patients (27.5%). This can be compared to studies of De BK et al., [95] Rao MY et al. [96]

Presenting complaint

Among the presenting complaints, abdominal distension was most common symptom present in 30 patients (75%).

The most common respiratory symptom was cough present in 10 patients (25%) followed by breathlessness in 7 patients (17.5%)

Clinical signs:

Out of 40 patients studied, 38 patients (95%) had Splenomegaly, 30 patients (75%) had ascites. Clubbing was present in 13 patients (32.5%), cyanosis in 4 patients (10%) and spider naevi in 8 patients (20%). Splenomegaly was the significant finding in patients of cirrhosis and it indicates the presence of portal hypertension.

Child-Pugh class:

In our study, out of 40 patients, 20 patients (50%) were in class B, 12 patients (30%) were in class C and 8 patients (20%) were in class A. Majority of patients were in class B. Child-Pugh class is a good indicator of the severity of liver disease. It is used to assess the patients for liver transplantation

Respiratory system examination findings

In respiratory system pleural effusion was the commonest examination finding present in 10 patients (25%). Right sided pleural effusion was more common. This was similar to study conducted by Hourani et al.[97]

Chest X ray findings

The most common radiographic finding was Right sided pleural effusion seen in 7 patients (17.5%) followed by bilateral pleural effusion in 2 patients (5%) and left sided pleural effusion in 1 patient (2.5%). This finding was similar to that seen in the study of Hourani et al.[97]

Endoscopic findings

The most common endoscopic finding was Grade 1 varices present in 17 patients (42.5%) followed by Grade 2 varices in 16 patients (40%) and Grade 3 varices in 7 patients (17.5%)

Hypoxemia

Out of 40 patient, 7 patients (17.5%) showed hypoxemia with PaO2 <70 mm Hg which was comparable to a study of Lange P A et al.[98]

Clinical signs of hypoxemia like cyanosis was present in 4 patients (10%), orthodeoxia in 4 patients (10%) which were similar to the finding observed by Krowka et al.[38]

The correlation between partial pressure of oxygen (PaO_2) and grading of oesophageal varices was done in this study. It was observed that there was a decrease in PaO2 with higher grade of varices. This was statistically significant with p-value of 0.01. It was similar to the observations in the study of Zhang HY et al and Schenk P et al

The correlation between PaO2 and severity of liver disease was also done. It was observed that there is progressive decrease in PaO2 with

increasing severity of liver disease. This was statistically significant in our study. PaO2 was more decreased in patients with Child-Pugh class C than other classes.

Pulmonary function tests

In pulmonary function tests, a restrictive pattern was the most common abnormality present in 11 patients (27.5%). A restrictive pattern of PFT could be observed in 25% of cases while 3.4% cases have an obstructive pattern. The above observation in our study was similar to the study of Rao MY et al.[96]

The correlation between predicted values of Forced Expired Volume in One Second (FEV1) with grading of varices as well as with the severity of liver disease was done in this study. It was observed that no significant correlation exists between predicted values of FEV1 and grading of varices & severity of liver disease.

HPS – Hepatopulmonary syndrome

Out of 40 patients in our study, HPS was identified in 4 patients (10%). All 4 patients had hypoxemia (PaO2 <70 mm Hg) and intra pulmonary shunting as established by contrast echo. They all had varices indicating portal hypertension. Hence increased portal venous pressure is a significant factor for development of HPS. The prevalence of HPS in cirrhotics in this study was comparable to studies conducted by Schenk P et al.,[2] Krowka et al.,[38] De BK et al.,[95] Rao MY et al.,[96] and Hourani et al.[97]

Orthodeoxia was present in all 4 patients who had HPS. All 4 patients of HPS had spider angiomas. This can be compared with other studies including De BK et al.,[95] Hourani et al.,[97] and Krowka et al.[38]

In this study correlation between prevalence of HPS and severity of liver disease was done. It was observed that prevalence of HPS was increased with the increasing severity of liver disease. All 4 patients of HPS in this study were under Child-Pugh class C.

CONCLUSION

CONCLUSION

Following results were concluded from our study:

- Cirrhosis of liver was more commonly seen in middle aged adults (in 4^{th} decade) and is common in males than females with male to female ratio of 3:1
- The most common pulmonary complaint was cough followed by breathlessness. Pleural effusion was the most common respiratory system finding observed.
- The most common chest radiographic abnormality was the right sided pleural effusion followed by cardiomegaly and bilateral pleural effusion.
- Restrictive pattern of lung disease was the most common abnormality detected by pulmonary function tests in cirrhosis
- Grade 1 varices was the most common endoscopic finding.
- Majority of patients were in the Child-Pugh class B.
- Significant correlation was observed between PaO2 and grading of varices. Pao2 was found to be decreased with higher grade of varices.

- Significant correlation was observed between PaO2 and severity of liver disease (Child-Pugh class). Pao2 was found to be decreased with increasing severity of liver disease. Hypoxemia was more common in class C followed by class B
- Hepatopulmonary syndrome (HPS) was the important complication present in patients with hypoxemia. All patients with hypoxemia had portal hypertension. It is a significant factor for development of hypoxemia.
- Cyanosis, orthodeoxia and spider naevi were observed in all patients of HPS
- HPS was most commonly seen in patients with Child-Pugh Class C.
- There was a significant correlation between the prevalence of HPS among cirrotics and the severity of liver disease.

SUMMARY

SUMMARY

Development of pulmonary manifestations of cirrhosis has several clinical implications with regard to their management, since they carry a poor prognosis.

Diagnosis of HPS needs a high index of suspicion among cirrhotics. As the prognosis of HPS poor, all patients with cirrhosis of liver must be screened for the presence of hypoxemia and HPS. The only proven treatment for HPS is liver transplantation.

All patients with HPS showed hypoxemia and intrapulmonary shunting on contrast echocardiogram. The clinical markers of hypoxemia such as cyanosis, orthodeoxia were seen in all patients of HPS. All the patients with HPS had esophageal varices indicating the presence of portal hypertension. Elevated portal pressure probably is a significant factor for the development of HPS.

Hypoxemia worsens with higher grade of varices and increasing severity of liver disease. Significant correlation exists between HPS prevalence and severity of liver disease. HPS is commonly underdiagnosed. Screening for HPS is important in patients with cirrhosis of liver.

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ANNEXURES

"PREVALENCE OF HEPATOPULMONARY SYNDROME IN PATIENTS WITH CIRRHOSIS OF LIVER"

PROFORMA

NAME: **AGE/SEX:**

ADDRESS: **OCCUPATION:**

PRESENTING COMPLAINTS:

- Abdominal distension
- Yellowish discolouration of eyes
- Swelling of legs
- Breathlessness
- Easy fatiguablity
- Cough with expectoration
- Others

PAST HISTORY:

- Ischemic heart disease
- Hypertension
- Diabetes
- Pulmonary TB
- Bronchial asthma
- Blood transfusion
- Jaundice

PERSONAL HISTORY:

- Smoking
- Alcohol

GENERAL EXAMINATION:

- Built
- Nourishment
- Height
- Weight

- Pallor
- Icterus
- Clubbing
- Cyanosis
- Pedal edema
- Lymphadenopathy
- Jugular venous pulse
- Signs of Liver cell failure

VITAL SIGNS:

- PR-
- BP-
- RR-

SYSTEMIC EXAMINATION:

- **PER ABDOMEN:**
- **CARDIOVASCULAR SYSTEM:**
- **RESPIRATORY SYSTEM:**
- **CENTRAL NERVOUS SYSTEM:**

INVESTIGATIONS:

- Complete hemogram
- Liver function tests
- Renal function tests
- USG abdomen
- Chest X-ray
- ECG
- Echocardiogram
- Viral markers
- Arterial blood gas analysis
- Pulmonary function tests

INFORMATION SHEET

We are conducting a study on **"PREVALENCE OF HEPATOPULMONARY SYNDROME IN PATIENTS WITH CIRRHOSIS OF LIVER"** among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study is to assess the pulmonary manifestations in patients with cirrhosis with the following factors Age, Sex, Presenting Complaints, Etiology of cirrhosis, Clinical findings, Chest X ray findings, Endoscopy findings, Arterial blood gas analysis, Pulmonary function test, Echocardiographic findings.

We are selecting certain cases and if you are found eligible, we may be using your blood samples to do certain tests which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator Signature of Participant

Date :
Place :

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு

கல்லீரல் இழைநார் வளர்ச்சி நோயினால் நுரையீரலில் ஏற்படும் பாதிப்புகள் குறித்த ஆராய்ச்சி.

பெயர்	:	தேதி	:
வயது	:	உள் நோயாளி எண்	:
பால்	:	ஆராய்ச்சி சேர்க்கை எண்	:

இந்த ஆராய்ச்சின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்துகொண்டு எனது சம்மதத்தை தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின்பேரில் பங்கு பெறுகின்றேன். இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்துகொண்டேன்.

நான் இந்த ஆராய்ச்சியின் விபரங்களைக் கொண்ட ஆராய்ச்சித் தகவல் தாளைப் பெற்றுக் கொண்டேன்.

இதன் மூலம் எந்த பின்விளைவும் ஏற்படாது என்று மருத்துவர் மூலம் தெரிந்து கொண்டு, நான் என்னுடைய சுய நினைவுடனும் மற்றும் முழு சுதந்திரத்துடனும் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக்கொள்ள சம்மதம் தெரிவிக்கிறேன்.

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நாள் :
இடம் :

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. Syed Ansari .J,
Post Graduate, MD (General Medicine)
Institute of Internal Medicine,
Madras Medical College,
Chennai – 600003.

Dear Dr. Syed Ansari .J,

The Institutional Ethics Committee has considered your request and approved your study titled **"Prevalence of Hepatopulmonary syndrome in patients with Cirrhosis of Liver"** No. 32072014.

The following members of Ethics Committee were present in the meeting held on 01.07.2014 conducted at Madras Medical College, Chennai-3.

1.	Dr. C. Rajendran, M.D.	-- Chairperson
2.	Dr. R. Vimala, M.D., Dean, MMC, Ch-3.	-- Deputy Chair Person
3.	Prof. Kalaiselvi, MD., Vice-Principal, MMC, Ch-3	-- Member Secretary
4.	Prof. Nandhini, M.D. Inst. of Pharmacology, MMC, Ch-3.	-- Member
5.	Dr. G. Muralidharan, Director Incharge , Inst. of Surgery	-- Member
6.	Prof. Md Ali, MD., DM., Prof & HOD of MGE, MMC, Ch-3.	-- Member
7.	Prof. Ramadevi, Director i/c, Biochemistry, MMC,Ch-3.	-- Member
8.	Prof. Saraswathy, MD., Director, Pathology, MMC, Ch-3.	-- Member
9.	Prof. Tito, Director, i/c. Inst. of Internal Medicine, MMC	-- Member
10.	Thiru. Rameshkumar, Administrative Officer	-- Lay Person
11.	Thiru. S. Govindasamy, BABL, High Court, Chennai-1.	-- Lawyer
12.	Tmt. Arnold Saulina, MA MSW	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

MASTER CHART

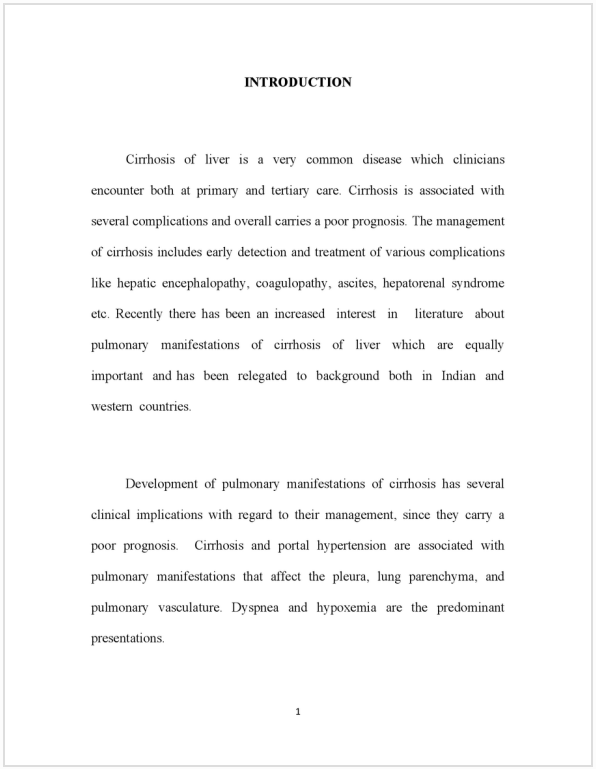
“PREVALENCE OF HEPATOPULMONARY SYNDROME IN PATIENTS WITH CIRRHOSIS OF LIVER”

MASTER CHART

S.No	Age	Sex	IP.No	Alcohol intake	Icterus	Pallor	Clubbing	Cyanosis	Orthodeoxia	Pedal edema	Spider naevi	Respiratory system	CVS	Ascites	Splenomegaly	Hemoglobin (gm%)	Serum bilirubin (mg%)	Serum albumin (gm%)	PT/INR	Viral markers	Chest x-ray	Upper GI endoscopy	Child Pugh class	ABG			PFT				Contrast Echo
																								PaO2	PCO2	Sao2	FEV1	FVC	PEFR	PFT pattern	
1	25	M	25736	+	-	-	+	-	-	+	-	PLE	N	+	+	9.2	2.1	2.4	16.5/1.4	Neg	RPE	EV G3	B	86	40	96	89.3	87.2	96	N	N
2	36	M	27206	+	+	-	+	-	-	-	-	N	N	-	+	10.2	4.3	3.1	12.9/1.2	Neg	N	EV G2	B	84	42	98	54	49.2	40.8	R	N
3	56	M	28299	-	+	-	-	-	-	-	-	N	N	-	+	9.6	4.4	2.6	15.4/1.4	Neg	N	EV G1	B	72	32	90	78.2	80.1	80	N	N
4	35	M	28429	+	+	+	-	-	-	+	-	PLE	ESM	+	+	6.5	3.2	2.8	14.4/1.4	Neg	RPE	EV G1	B	82	36	96	90	96	97	N	N
5	40	F	31034	-	+	-	-	-	-	+	-	N	N	+	+	8.9	2.8	3.0	18.6/1.7	Neg	N	EV G1	B	81	35	88	76	80.2	82	N	N
6	51	M	33519	+	+	+	+	-	-	-	+	N	N	+	+	8	3.9	3.2	15.4/1.5	Neg	N	EV G2	C	86	40	92	90	86.4	86	R	N
7	45	M	36045	+	+	-	-	-	-	+	-	PLE	N	+	+	10.6	2.5	3.1	13.3/1.0	Neg	RPE	EV G2	B	78	41	91	96	90.2	86	N	N
8	26	M	36113	+	-	-	-	-	-	-	-	N	N	-	+	11.2	1.2	3.4	16.5/1.5	Neg	N	EV G2	A	81	41	90	98	90.1	98	N	N
9	43	F	38378	-	+	+	-	-	-	+	-	N	ESM	+	+	6.7	2.2	2.5	14.4/1.3	HBV	CM	EV G1	B	77	36	88	84.2	82.6	80.1	N	N
10	55	M	40375	+	+	-	+	+	+	+	+	N	N	+	+	9	3.4	2.1	16.4/1.4	Neg	N	EV G3	C	60	34	84	72.5	68.1	76.2	R	IPS
11	40	M	40545	-	-	-	-	-	-	-	-	N	N	-	+	10.4	1.4	3.5	17.6/1.6	Neg	N	EV G2	A	72	40	90	90	92.3	95.1	N	N
12	54	M	40513	+	+	-	-	-	-	+	-	PLE	N	+	+	11	4.6	2.0	18.1/1.8	Neg	RPE	EV G2	C	81	42	91	96	96	95	N	N
13	60	M	45739	+	+	-	+	+	+	+	+	N	N	+	+	9.5	6.5	2.9	19.9/2.1	Neg	N	EV G2	C	68	35	82	76.2	74	80	R	IPS
14	44	M	47099	-	-	-	-	-	-	-	-	N	N	-	-	10.2	1.3	3.0	15.7/1.4	Neg	N	EV G1	A	80	42	96	86.2	84.2	90	N	N
15	30	F	48193	-	-	+	+	-	-	+	-	N	ESM	+	+	7.2	1.2	3.2	16.6/1.6	Neg	N	EV G2	A	86	45	96	62.1	60	76.2	R	N
16	27	M	48390	+	+	-	-	-	-	+	+	PLE	N	+	+	9.8	3.2	2.4	15.6/1.4	Neg	RPE	EV G2	C	76	38	96	88.2	90.2	92.2	N	N
17	42	M	48192	+	+	-	-	-	-	-	-	N	N	+	+	10.4	4.1	2.8	14.9/1.4	Neg	N	EV G1	B	72	36	90	80.2	82.2	96.2	N	N
18	40	F	51171	-	-	+	-	-	-	+	-	PLE	ESM	+	+	7	2.0	3.0	16.3/1.5	HBV	BPE	EV G1	B	81	41	92	88.2	90.2	92.2	N	N

19	35	M	53683	+	+	-	-	-	-	+	-	PLE	N	+	+	9.8	3.1	2.6	16.3/1.5	Neg	LPE	EV G1	C	82	42	93	90.2	92.2	86.2	N	N
20	35	F	53651	+	+	+	-	-	-	+	-	N	ESM	+	+	6.6	2.8	3.2	14.5/1.3	Neg	CM	EV G1	C	81	36	93	92.2	94.6	96.2	N	N
21	40	M	53608	-	+	-	-	-	-	+	-	PLE	N	+	+	10.2	3.2	3.0	13/0.9	HCV	RPE	EV G1	B	77	41	96	96.2	98.2	98	N	N
22	65	F	56309	+	+	-	+	-	-	-	-	N	N	-	+	10	4.1	2.8	15.2/1.4	Neg	N	EV G2	B	78	39	94	68.5	56	50.8	R	N
23	52	M	56561	-	+	-	+	+	+	+	+	N	N	+	+	10.5	5.2	2.1	19.6/2.0	Neg	N	EV G3	C	63	35	86	76	70.5	77.2	R	IPS
24	46	M	58972	-	+	-	-	-	-	+	-	N	N	+	+	11	3.2	2.7	14.3/1.2	Neg	N	EV G1	B	72	35	88	80.7	80.6	78.1	N	N
25	38	M	59051	+	+	-	-	-	-	+	-	N	N	+	+	10.2	4.1	3.0	15.1/1.3	Neg	N	EV G2	B	78	36	90	89.2	90.2	90.1	N	N
26	34	M	61760	+	+	-	+	-	-	-	-	N	N	-	+	11.4	3.0	2.2	15.3/1.4	Neg	N	EV G1	C	72	37	91	90.2	91.2	90.4	N	N
27	48	F	64300	-	-	+	-	-	-	-	-	N	ESM	-	+	7	1.2	3.0	16.8/1.5	Neg	N	EV G3	A	80	36	90	91.2	86.2	90.1	N	N
28	50	F	64210	+	+	+	-	-	-	+	-	PLE	ESM	+	+	5.6	3.1	2.4	14.7/1.3	Neg	BPE	EV G1	B	77	41	94	96.2	98.2	96	N	N
29	55	M	64404	+	+	-	-	-	-	+	-	N	N	+	+	10	2.1	2.6	13.1/1.2	Neg	N	EV G1	B	82	40	99	90.2	90.2	90.5	N	N
30	26	M	64392	-	+	-	+	-	-	-	+	N	N	+	+	9.2	4.2	3.0	14.6/1.3	HCV	N	EV G2	C	66	35	81	74.1	72.2	76	R	N
31	42	F	67062	-	-	+	-	-	-	+	-	N	ESM	+	+	6.3	1.6	2.2	15.1/1.3	Neg	N	EV G1	B	81	41	96	86.2	90.8	98	N	N
32	40	M	72070	+	+	-	+	+	+	+	+	N	N	+	+	9.6	4.8	3.1	16.9/1.6	Neg	N	EV G2	C	64	32	84	76.2	76	62	R	IPS
33	70	M	74812	+	+	+	-	-	-	+	-	N	ESM	+	+	5.2	2.2	2.6	16.1/1.4	Neg	N	EV G3	B	80	42	96	96.2	98.2	98	N	N
34	36	M	75498	+	+	-	-	-	-	-	-	N	N	-	+	9.2	2.6	2.8	17.8/1.4	Neg	N	EV G1	A	78	43	96	96.2	97.0	96	N	N
35	55	M	76549	+	+	-	-	-	-	+	+	PLE	N	+	+	9.5	3.8	2.6	16.4/1.3	Neg	RPE	EV G3	C	90	39	96	90.2	86.1	90.2	N	N
36	51	M	77233	-	+	+	+	-	-	-	-	N	ESM	-	+	6.3	4.2	3.0	13.4/1.2	Neg	CM	EV G2	B	68	34	78	80	76	68	R	N
37	29	M	77274	+	+	-	-	-	-	-	-	N	N	+	+	10.2	3.4	2.8	14.6/1.4	Neg	N	EV G2	B	84	40	90	86.2	84.2	86	N	N
38	45	M	77292	-	+	-	+	-	-	-	-	N	N	+	+	9.8	2.8	3.2	16.2/1.5	Neg	N	EV G3	B	63	33	81	70.1	70	68	R	N
39	37	M	80033	-	+	+	-	-	-	+	-	N	ESM	+	+	6	2.1	2.9	15.1/1.4	HBV	N	EV G2	A	77	45	90	98.2	98.2	95	N	N
40	45	M	80073	+	-	-	-	-	-	+	-	N	N	+	-	9.6	1.5	3.0	13.4/1.2	Neg	N	EV G1	A	78	44	96	98.2	98	94	N	N

CVS-cardiovascular system, PLE-pleural effusion, ESM-ejection systolic murmur, HBV-hepatitis B virus, HCV-hepatitis C virus, Neg-negaitve, RPE-right pleural effusion, LPE-left pleural effusion,BPE-bilateral pleural effusion, CM-cardiomegaly, EVG-esophageal varices grading, N-normal, R-restrictive lung disease, IPS-intrapulmonary shunting

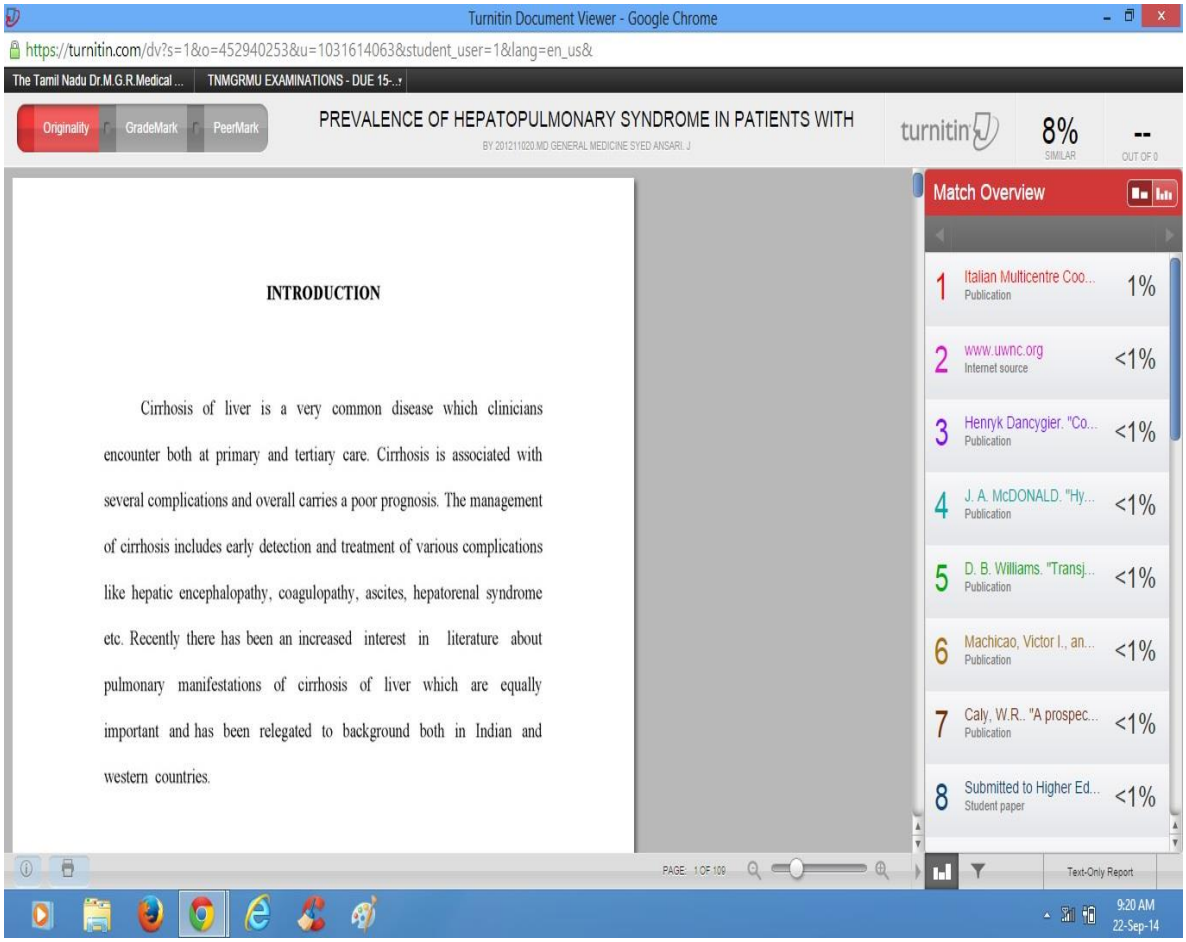


INTRODUCTION

Cirrhosis of liver is a very common disease which clinicians encounter both at primary and tertiary care. Cirrhosis is associated with several complications and overall carries a poor prognosis. The management of cirrhosis includes early detection and treatment of various complications like hepatic encephalopathy, coagulopathy, ascites, hepatorenal syndrome etc. Recently there has been an increased interest in literature about pulmonary manifestations of cirrhosis of liver which are equally important and has been relegated to background both in Indian and western countries.

Development of pulmonary manifestations of cirrhosis has several clinical implications with regard to their management, since they carry a poor prognosis. Cirrhosis and portal hypertension are associated with pulmonary manifestations that affect the pleura, lung parenchyma, and pulmonary vasculature. Dyspnea and hypoxemia are the predominant presentations.

1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